Chronic Lymphocytic Leukemia in the Elderly: Epidemiology and Proposed Patient-Related Approach

Chronic Lymphocytic Leukemia in the Elderly, Which Investigations Are Necessary: A Map for the Practicing Oncologist

Management of Chronic Lymphocytic Leukemia in the Elderly
Table of Contents

Editorial

Why a Special Issue on Chronic Lymphocytic Leukemia?  
Lodovico Balducci, MD  
2

Articles

Chronic Lymphocytic Leukemia in the Elderly:  
Epidemiology and Proposed Patient-Related Approach  
Lodovico Balducci, MD, and Dawn Dolan, PharmD  
3

Chronic Lymphocytic Leukemia in the Elderly,  
Which Investigations Are Necessary: A Map for the Practicing Oncologist  
Javier Pinilla-Ibarz, MD, PhD, and Josephine Emole, MD  
7

Management of Chronic Lymphocytic Leukemia in the Elderly  
Jacqueline C. Barrientos, MD  
17

About the art in this issue:

Lisa Scholder is a multimedia artist whose canvas is the human body. Her technique involves applying body paint onto nude models, then digitally photographing the painted body. The explosion of illuminating color on the human form is Scholder’s artistic trademark. All of the models shown in this issue are breast cancer survivors of varying ages and body types, and they are part of the Bodies of Courage project.

Scholder takes several hours to hand-paint the model with a crème-based paint and often incorporates other body-painted images in the final piece, which does not include the face of her model. Her artwork focuses on the abstract portrayal of the body infused with vibrant colors. Scholder’s late father-in-law, renowned Indian artist Fritz Scholder, had an unmistakable influence on her bold color combinations. Each model’s unique strength is represented with abstract and, at times, expressionist art forms on her body. The artist’s driving force is the self-empowerment that this process can bestow on her model, enabling her to see her body as a colorful, unique piece of art.

With no formal art training, she began body painting in 2000 and developed her distinct body painting and photography style. Her first public exhibition was in 2004, and she has progressed to gallery and art museum exhibitions.

“Bodies of Courage” is an Arts in Medicine project (www.bodiesofcourage.org) in partnership with the Faces of Courage Foundation (www.facesofcourage.org), which provides at no cost day outings and overnight camps for women, children, and families diagnosed with any type of cancer. Lisa Scholder and Peggie D. Sherry, the founder of Faces of Courage, began this project 5 years ago as a way to raise awareness and as an artistic therapy for cancer survivors. This project is an artistic testimony to the strength and determination of these survivors throughout their battles with cancer, their celebration of life, and their reconnection with the beauty of their own bodies.

For information about the traveling gallery, please contact Peggie D. Sherry at psherry@facesofcourage.org or (813) 948-7478. Further information on these projects is available at www.bodiesofcourage.org and www.facesofcourage.org.

Cover:  
Self Hug Sit. 12” × 18”

Articles:  
Color Sphere. 12” × 18”
Yellow Star Port. 14” × 24”
Sunflower. 16” × 24”

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Editorial

Why a Special Issue on Chronic Lymphocytic Leukemia?

The aging of the population, which has been called the “gray tsunami,”1 has at least three important implications for the practice of oncology:

- It is associated with increased incidence and prevalence of neoplastic diseases in general and in older individuals in particular.
- The ongoing prolongation of the average life expectancy of residents of developed countries has changed the impact of cancer on the survival of older patients. Whereas in the past most older individuals diagnosed with chronic lymphocytic leukemia (CLL) or prostate cancer might have died with the disease but of other causes, nowadays they are more likely to die as a direct consequence of these neoplasms.2-3
- How to treat neoplastic diseases in older individuals is becoming a progressively more common concern among healthcare providers.4

CLL is an appropriate model to explore these issues, as age is universally recognized to be a poor prognostic factor for CLL,2 and novel agents promise to modify the natural history of the disease.5-6 Some of these agents—including ibrutinib, idelalisib, obinutuzumab, and ofatumumab—lack major toxicities and therefore are particularly promising for older individuals. Aging represents a progressive loss in the functional reserve of multiple organ systems and for that reason is associated with reduced tolerance of stress. Consequently, some of the most effective treatments for CLL, such as the combination of fludarabine, cyclophosphamide, and rituximab (FCR) or bone marrow transplant in 17p deleted/TP53-mutated disease may be contraindicated in the majority of individuals 70 years of age and older.5-6

After an overview of the epidemiology2 and treatment strategies6 for CLL, this special issue of Cancer Control examines the approach to CLL in older individuals.5 As expected in a scientific treatise, new conclusions and new questions are offered.

The most important conclusions include:

- CLL is lethal for the majority of older individuals who develop it before age 80, and there are reasons to believe that it may be lethal even up to age 85.2
- New agents—including obinutuzumab, ofatumumab, ibrutinib, and idelalisib—have improved the survival of older individuals, even among those affected with moderate comorbidity.2,5-6
- Ibrutinib is the only approved agent for patients with 17p deleted/TP53-mutated disease, and it may be life-saving for older individuals with this type of CLL. Idelalisib is also promising in this context.

The most important questions include:

- Should clinicians try to achieve a condition of minimal residual disease (MRD) in older CLL patients? Is MRD predictive of survival in patients treated with novel agents compared with those treated with cytotoxic chemotherapy? How can the benefit of MRD best be determined in older individuals with limited life-expectancy and treatment tolerance?
- Can the novel agents achieve the same results, and with decreased toxicity, as FCR or bendamustine plus rituximab (BR) in older individuals?
- What are the long-term complications of these novel treatments? Since treated CLL patients may have a life expectancy of longer than a decade, the late complications of treatment are particularly relevant to their survival and quality of life.

Overall, this supplement invites readers to feel a sense of cautious optimism for the outcome of CLL in older individuals, and this optimism should be reinforced by the ongoing development of new, less toxic and more efficacious, albeit more expensive, treatment modalities.

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References

More accurate tools to assess frailty and physiologic age will play an increasingly important role in the management of elderly chronic lymphocytic leukemia patients.

Chronic Lymphocytic Leukemia in the Elderly: Epidemiology and Proposed Patient-Related Approach

Lodovico Balducci, MD, and Dawn Dolan, PharmD

Background: Chronic lymphocytic leukemia (CLL) occurs primarily in the elderly, and the majority of deaths attributable to CLL occur in persons 65 years of age or older. The greater number of comorbidities and reduced functionality associated with aging have also made successful treatment of CLL in the elderly more difficult.

Methods: The authors reviewed current epidemiology and guidelines for treatment of CLL, as well as recently approved therapies and studies of physiological aging.

Results: Determination of physiological age and performance of a thorough geriatric assessment play critical roles in the selection of optimal therapeutic approaches for older patients diagnosed with CLL.

Conclusion: Older age, expressed via a frailty index, is a prognostic factor for poorer outcome in patients with CLL. However, several novel treatment options may result in reduced mortality and lessened treatment-related toxicity in older CLL patients.

Introduction

Chronic lymphocytic leukemia (CLL) is a disease of aging. According to the most recent statistics, there are approximately 15,000 new cases of CLL in the United States every year, and half of them occur in individuals 71 years and older. Persons 65 years of age and older account for 60% of the annual deaths attributed to CLL and for 70% of the approximately 150,000 CLL patients currently alive. With the rapid aging of the population, the incidence and prevalence of CLL among older persons may be expected to continue to increase. In addition, treatment advances that are prolonging the survival of the majority of patients will contribute to increased CLL survival in this population.

This article reviews the influence of CLL on the life expectancy and the function of older individuals and appropriate treatment strategies for them.

CLL and Life Expectancy

Contrary to a common impression, the majority of older CLL patients die of the disease rather than with it. Age has been shown to be an independent adverse factor for survival in two prognostic models (Table 1). In a group of Israeli patients, Bairey et al demonstrated that age greater than 80 years was associated with poorer CLL-specific survival vs younger individuals. In a review of 2,487 cases of CLL diagnosed at the Mayo Clinic between 1995 and 2008, Shanafelt et al reported that age at diagnosis was an independent prognostic factor for survival. Even patients with Rai stage 0 at diagnosis had a shorter survival than individuals of the same age without CLL, indicating that CLL is indeed a
mortality risk for the elderly.

Particularly relevant to this discussion is the study by Goede et al, which randomized CLL patients with multiple comorbidities and mean age of 73 years to receive chlorambucil, chlorambucil plus rituximab, or chlorambucil plus obizutunumab. The investigators found that the combination including obizutunumab led to greater overall survival and progression-free survival. This important study further confirms that CLL is a cause of mortality in patients with advanced age and substantial comorbidity. All of the patients recruited into the study had well-established treatment indications.

These findings raise the question of whether poorer survival in older patients is due to the biology of the disease or to poorer treatment tolerance. Bulian et al and Shanefelt et al demonstrated that age was a prognostic factor for poorer survival independent of the absence of immunoglobulin heavy chain variable (IGHV) mutation and of the p17 deletion. Moreover, whether age is associated more frequently with ZAP-70, CD38, q11 deletion disease, or more frequent Richter’s transformation remains undetermined at this time.

A recent study by the International Myeloma Study Group showed that the frailty index — which is derived from the prevalence and severity of comorbidity and functional dependence — was associated with decreased tolerance of chemotherapy and poorer survival in patients with multiple myeloma. The findings of this study may imply that poor treatment tolerance may be responsible for decreased survival even in older patients with CLL.

This brief review suggests the following conclusions:

- CLL is a cause of death for older individuals, especially for those aged 80 years and older. Older individuals may benefit from more effective, novel treatment of CLL.
- Age is associated with poor prognosis in CLL patients, with age and prognosis correlated at least up to 85 years of age.
- Age does not appear to be associated with decreased prevalence of either IGHV mutation or increased prevalence of p17 deletion. No information is available concerning the association of age with CD38, ZAP-70, 11q deletion, or risk of Richter’s transformation.
- Physiologic age, expressed as a frailty index, is associated with poor treatment tolerance; this may explain, in part, the poorer CLL prognosis in patients of advanced age.

### Personalization of Treatment in Older Chronic Lymphocytic Leukemia Patients

The assessment of physiological age, its influence on treatment tolerance, and personalized treatment of CLL are emerging as key issues in the management of CLL in older patients. Figure 1 illustrates the interaction of disease, age, and treatment in therapeutic decision making. Aging involves a progressive decline in functional reserve and increased polymorbidity that combine to reduce a person’s life expectancy and tolerance of stress. These changes are universal but occ...
cur at different rates in different individuals so that a person's chronological age is a poor indicator of physiological age. The determination of life expectancy and functional reserve is essential to estimate the risks and benefits of CLL treatment for older patients. Table 2 presents the key factors to be considered in assessing a person's physiological age. Laboratory tests have limited value for this purpose. Although the length of leukocyte telomeres decreases progressively with age, a high degree of inter-personal variability prevents the use of this test for the determination of individual physiological age.11

The “inflammatory index” was developed in a large cohort study, the Chianti study, and was validated in the Baltimore Longitudinal Study. It is well established that aging is a progressive inflammatory process, as the concentration of different inflammatory markers increases in the circulation with aging.12 The concentration of these substances also predicts the likelihood of aging-related events, including death, disability, and memory disorders. Varadhan et al12 found that the sum of the logarithm of the concentration of interleukin 6 (IL-6) plus the logarithm of the concentration of tumor necrosis factor receptor 1 in the circulation more accurately predicted the risk of mortality at 10 years than any other combination of inflammatory markers. However, these data were obtained in patients who had not been diagnosed with cancer, and how cancer-induced inflammation may affect the prediction remains unclear. The expression of p16INK4a in mesenchymal tissues may reflect the tissue’s age, but to make this determination requires a biopsy. However, this has not yet been validated in a large group of individuals.13

The best-validated estimate of physiological age at present derives from a comprehensive geriatric assessment that includes function, polymorbidity, polypharmacy, cognitive and emotional status, social support, nutrition, and financial resources. A combination of these factors allows clinicians to predict the risk of mortality in older individuals up to nine years in the future.14 Two indices predicting the risk of cytotoxic chemotherapy-related toxicity are based on the geriatric assessment.15,16 Other benefits of geriatric assessment include disclosure of other conditions that may interfere with cancer treatment such as undiagnosed diseases, drug interactions, memory disorders, depression, malnutrition, and inadequate social support.17 For these reasons, National Comprehensive Cancer Network (NCCN) guidelines recommend that a comprehensive geriatric assessment should be part of the initial evaluation of older cancer patients.17

Establishing the goal of treatment is important for every patient with an incurable disease but especially for older individuals whose treatment options may be more limited due to reduced functional reserve.18 A realistic appreciation of the benefits and risks of treatment is essential to establish realistic goals. Prolongation of an individual’s active life expectancy, i.e., of functional independence, is a major goal for older cancer patients, and that goal may be of even greater importance than the prolongation of survival.10 The risk of some forms of chemotherapy-related toxicity increases with a patient’s age.10,17 Among these risks, myelosuppression and neutropenic infections are the most common — and the most lethal. Most clinicians agree that myelopoietic growth factors should be used prophylactically in individuals 65 years and older who are receiving chemotherapy that has a dose-intensity comparable to that of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone).17,19

The risk of chemotherapy-induced neuropathy and cardiomyopathy also increases with age. Peripheral neuropathy may result from a number of chemotherapy agents and may cause severe functional impairment.20

In a disease with prolonged survival, such as CLL, long-term toxicity is also important. In addition to neuropathy, such toxicities may include fatigue and memory disorders.21 Fatigue in older cancer patients is a harbinger of functional dependence and ultimately of mortality. Although there is no definitive proof that cytotoxic chemotherapy may cause dementia in older individuals, it may cause troublesome memory disorders that can precede progressive deterioration of quality of life and independence.21

**Conclusion**

CLL is a disease of aging, and its incidence and prevalence are expected to increase with the aging of the population. Moreover, age is a poor prognostic factor for CLL, independent of lack of IGHV mutation and of

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<thead>
<tr>
<th>Table 2. — Assessment of Physiologic Age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory Assessments</strong></td>
</tr>
<tr>
<td>Length of leukocyte telomeres</td>
</tr>
<tr>
<td>Inflammatory index</td>
</tr>
<tr>
<td>Tissue expression of p16INK4a</td>
</tr>
<tr>
<td><strong>Comprehensive Clinical Geriatric Assessment</strong></td>
</tr>
<tr>
<td>Function expressed as performance status, activities of daily living (ADLs), and instrumental activities of daily living (IADLs)</td>
</tr>
<tr>
<td>Polymorbidity expressed as the number of diseases and as comorbidity index</td>
</tr>
<tr>
<td>Polypharmacy expressed as the number of drugs, potential drug interactions, and inappropriate prescriptions</td>
</tr>
<tr>
<td>Cognitive screening</td>
</tr>
<tr>
<td>Nutritional screening</td>
</tr>
<tr>
<td>Depression screening</td>
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<tr>
<td>Socioeconomic resources</td>
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October 2015, Vol. 22, No. 4 Supplement Cancer Control  5
17p deletion. The relation between aging and ZAP-70, CD38, 11q deletion disease, and Richter’s transformation is unknown. CLL is the leading cause of death for older individuals who have been diagnosed with the disease. A number of new treatment options — including obizutunumab, ibrutinib, and idelalisib — may allow clinicians to prevent or delay CLL-related death in older individuals without life- or function-threatening toxicity.

References
The findings of recent clinical trials point toward improved patient outcomes for older chronic lymphocytic leukemia patients.

Chronic Lymphocytic Leukemia in the Elderly, Which Investigations Are Necessary: A Map for the Practicing Oncologist

Javier Pinilla-Ibarz, MD, PhD, and Josephine Emole, MD

Background: Chronic lymphocytic leukemia (CLL), the most prevalent leukemia in the Western world, is predominantly a disease of older individuals who also have other comorbidities as well as declining organ and bone marrow reserve. Although chemoimmunotherapy is the frontline therapy for fit CLL patients who can tolerate the therapy, many elderly patients cannot tolerate such intense therapy.

Methods: The authors first reviewed the most recent findings concerning CLL cytogenetics, molecular biology, and prognostic models. They then surveyed recent and ongoing trials of novel CLL agents and strategies, with a focus on those most relevant to elderly patients.

Results: Novel therapies, revised staging procedures, and careful assessment of individual patients’ frailty and functional status will allow clinicians to provide optimal care management for older CLL patients.

Conclusion: Therapy for the elderly CLL population must be tailored to each patient’s fitness level and co-morbid conditions, with special consideration for the potential quality-of-life impacts of various treatment recommendations.

Introduction

Chronic lymphocytic leukemia (CLL) is a monoclonal lymphoid malignancy characterized by a progressive accumulation of small, mature but functionally incompetent neoplastic lymphocytes in the peripheral blood, bone marrow, and lymphoid organs. The malignant lymphocytes in CLL are usually of B-cell lineage (CD5+, CD10–, CD19+, CD20 dim, and CD23+).

CLL is the most prevalent leukemia, accounting for approximately 25% to 30% of all leukemias in the Western world. The incidence of CLL is approximately 4.1 per 100,000 persons per year. In 2015, an estimated 14,620 persons will be diagnosed with CLL in the United States, and an estimated 4,650 persons will die of the disease (representing approximately 0.8% of all cancer deaths). The median age at diagnosis of CLL is 72 years, with approximately 70% of patients being ≥ 65 years and 40% ≥ 75 years old. CLL is rare in persons younger than 25 years of age. The prevalence of CLL is higher in Caucasians and males.

The clinical course of CLL can be variable. More than half of CLL patients are diagnosed at an early stage. Many CLL patients have an indolent course and neither develop symptoms nor require treatment for many years. For such patients, observation/watchful waiting is an appropriate management strategy. Other patients have a more aggressive course and die due to CLL within two to three years. Different prognostic features at diagnosis or at the time of progression of
CLL account for the heterogeneous patient outcomes in CLL, and these features are predictors of progression-free survival (PFS) and overall survival (OS). Patients with certain poor prognostic features are also more likely to be refractory to first-line treatment or to relapse early, thereby requiring salvage therapy.

Treatment modalities for CLL had historically focused on reducing tumor bulk, alleviating symptoms, and providing a good quality of life. Following its introduction in the early 1950s, chlorambucil became the mainstay of therapy for CLL. The advent of the anti-CD20 monoclonal antibody rituximab enabled combination therapy with rituximab plus a purine analogue and resulted in improved response rates in CLL. When chemoimmunotherapy consisting of fludarabine, cyclophosphamide, and rituximab (FCR) was shown to lead to a significant improvement in OS and PFS in a randomized phase 3 trial, FCR thereafter emerged as the standard therapy for physically fit patients and changed the goal of CLL therapy to obtaining a complete remission (CR). Since many elderly CLL patients may not tolerate such an aggressive therapy, there was need to tailor treatment goals for this population to the individual patient’s comorbidities and functional capacity. More recently, combination chemoimmunotherapy comprising either obinutuzumab or ofatumumab plus chlorambucil was approved by the US Food and Drug Administration (FDA) and may be more suitable for older patients with comorbidities.

Diagnosis and Workup

As many as one-quarter of CLL patients may be asymptomatic at diagnosis, when their disease is diagnosed incidentally upon detection of absolute lymphocytosis or enlarged lymph node(s). Other patients may present with nonspecific symptoms such as fatigue, malaise, decreased exercise tolerance, bleeding secondary to thrombocytopenia, or symptomatic anemia. Since CLL is characterized by impaired T-cell immunity and/or hypogammaglobulinemia, some patients may also present with recurrent viral or bacterial infections. Some patients with advanced disease at diagnosis may present with the classic “B symptoms” consisting of night sweats, fevers, and weight loss, but the onset of these symptoms in the setting of CLL relapse should raise suspicion of transformation to a high-grade lymphoma, ie, Richter’s transformation.

Before making a diagnosis of CLL, the presence of monoclonal B-cell lymphocytosis of ≥ 5,000/mcL (5 × 10⁹/L) in the peripheral blood must be established. Values below this should be categorized as monoclonal B-cell lymphocytosis when there is no associated lymphadenopathy. This distinction is important because patients with monoclonal B-cell lymphocytosis have a B-cell phenotype similar to CLL but with < 5,000/mcL (5 × 10⁹/L) monoclonal B-cells. This relatively new entity has a rate of transformation to CLL of 1% to 2% per year. Diagnosis of small lymphocytic leukemia (SLL) requires the presence of lymphadenopathy and/or splenomegaly but < 5 × 10⁹/L clonal B lymphocytes in the peripheral blood. This review will refer to both CLL and SLL as CLL.

Once absolute lymphocytosis that meets the diagnostic criteria for CLL is noted in the peripheral blood, a blood smear should be reviewed. Morphologically, CLL cells are small, mature-appearing lymphocytes with round nuclei, clumped chromatin, and scant cytoplasm. A flow cytometry of peripheral blood should be performed to confirm the clonality of the lymphocytes, using the expression profile for cell surface markers, including kappa/lambda, CD5, CD10, CD19, CD20, and CD23. Classic immunophenotype expression pattern for CLL is CD5+, CD10−, CD19+, CD20 dim, and CD23-. Classic immunophenotype expression pattern for CLL is CD5+, CD10−, CD19+, CD20 dim, and CD23-, and low expression of surface immunoglobulins. Florescence in situ hybridization (FISH) for t(11;14) is required to rule out mantle cell lymphoma (MCL), which shares many immunophenotypic features with CLL, except that MCL is characterized by CD23 negativity.

Cytogenetic evaluation and FISH for del(17p), del(11q), trisomy 12, del(13q), and genetic analysis for immunoglobulin heavy chain variable region (IGHV) mutational status and TP53 mutation should be done to provide prognostic (and predictive) information. These tests are not absolutely necessary for the initial diagnosis of CLL, but they should be implemented before initiation of therapy. Diagnosis of SLL requires a lymph node biopsy. A lymph node biopsy may also be necessary in a CLL patient to exclude transformation to high-grade lymphomas, especially in patients with rapidly enlarging lymph nodes.

Anemia and/or thrombocytopenia may occur at diagnosis in CLL due to marrow infiltration, autoimmunity against red cells and platelets, or hypersplenism. A bone marrow biopsy is not required to make a diagnosis of CLL but should be done to evaluate these cytopenias and before initiating CLL therapy. Reticulocyte count and Coombs tests are necessary for evaluation of immune hemolytic anemia and red cell aplasia, as both entities can be seen in CLL patients.

For patients with recurrent infections, IgG, IgA, and IgM levels should be measured. Computed tomography (CT) scans should not be routinely done at initial diagnosis or in asymptomatic patients, although they may be necessary to monitor disease progression in some patients with new symptoms. CT scans may also be necessary to evaluate patients with new-onset laboratory abnormalities if these abnormalities are suspected to be secondary to lymph node enlargement.

Prognostic Factors and Risk Stratification

Two systems (Rai and Binet) have traditionally been used to stage CLL. Both staging systems were based
on clinical and laboratory features such as the presence of lymphocytosis, lymphadenopathy, hepatosplenomegaly, anemia, or thrombocytopenia. Introduced by Rai and colleagues in 1975, the original Rai staging system classified patients into five clinical stages (0-IV). In 1981, Binet et al proposed a three-stage classification based on the overall lymphoid mass and presence of anemia or thrombocytopenia. In 1987, Rai modified the original Rai staging and classified patients into three risk groups: low, intermediate, and high risk.

In addition to the two major clinical staging systems, other prognostic factors have been proposed for better risk stratification of CLL, especially in early-stage patients. These additional prognostic factors include serum markers (thymidine kinase, beta-2 microglobulin), phenotype markers (CD38, ZAP-70, and CD49d), cytogenetic abnormalities (del(11q), del(17p), trisomy 12), and molecular characteristics (IGHV gene mutation) of the neoplastic B-cells. More recently the availability of next-generation technologies has identified a limited number of genetic mutations (NOTCH1, SF3B1, BIRC3, TP53) that may be associated with poorer outcomes. Some of these prognostic factors have been valuable in predicting likely disease progression as well as outcomes in untreated patients. Their utility in deciding when to initiate therapy or in predicting response to treatment has not yet been completely defined.

Immunoglobulin Heavy Chain Variable Region Gene Mutation

Immunoglobulin expressed on B-cells consists of light and heavy chains. The extent to which the genes encoding for the heavy chain variable region have undergone somatic mutation can be used to distinguish two groups of CLL patients: those with unmutated immunoglobulin heavy chain variable region gene (unmutated IGHV) and those with mutated genes (mutated IGHV). These two subsets have different propensities for progression, with the unmutated IGHV CLL cases having a higher tendency for rapidly progressive disease. In contrast, patients with IGHV genes of < 98% nucleic acid homology with germ-line counterpart (mutated IGHV) tend to have a slower and more stable course, except for the 3-21 family of IGHV mutated genes that has been associated with a worse outcome. CLL cases with unmutated IGHV tend to be associated with del(11q) and del(17p), whereas those with mutated IGHV tend to have trisomy 12 and 13q14 abnormalities. The IGHV mutational status does not predict response to treatment but is typically associated with shorter remission durations in patients with unmutated IGHV CLL treated with chemotherapy regimens compared with patients with mutated IGHV.

CD38

CD38 is a transmembrane glycoprotein that synthesizes cyclic adenosine diphosphate (ADP)-ribose from nicotinamide adenine dinucleotide and hydrolyses cyclic ADP-ribose to ADP-ribose. Some studies have suggested that increased expression of CD38 on the surface of CLL cells is associated with inferior outcomes.

Zeta-Associated Protein of 70kDa (ZAP-70)

ZAP-70 is a cytoplasmic tyrosine kinase that is usually highly expressed in natural killer cells and T-cells and is essential in receptor signaling in response to antigens. CLL cells with mutated IGHV genes usually do not express detectable levels of ZAP-70. In contrast, CLL cells with unmutated IGHV genes have relatively high expression of ZAP-70. Higher expression of ZAP-70 (as assessed by flow cytometry) has been found to predict more rapid disease progression, shorter time from diagnosis to treatment, and shorter OS.

CD49d

CD49d (α4 subunit of integrin heterodimer α4β1), is a surface molecule which, along with the α4 integrin, acts as adhesion structure for extracellular matrix components and mediates cell-cell interactions. Expression of CD49d promotes microenvironment-mediated proliferation of CLL cells. Increased CD49d protein expression has been demonstrated in CLL cells from advanced Rai stage patients (stages III and IV). CD49d expression has also been described to be a prognosticator for time to treatment initiation and OS. Compared with other flow cytometry-based prognostic factors (CD38 and ZAP-70), CD49d has been suggested as the strongest predictor of OS and treatment-free survival in CLL patients.

Cytogenetics

Deletion at 17p (del(17p)) is commonly associated with defects in TP53, a tumor suppressor gene that regulates a network that senses extracellular stress, oncogene activation, and DNA damage; TP53 also enables the cell to react to such stimuli either by cell cycle arrest or apoptosis. The gene encodes the P53 protein, which plays a role in the cytotoxic activity of many chemotherapy agents. Not all cases with del(17p) have loss of P53 function, and a concordance rate of 94% has been suggested between del(17p) and TP53 mutation. Relatively few (approximately 4.5%) patients without del17p may have a TP53 mutation by sequencing. TP53 mutations in CLL predict for poor prognosis and poor response to purine analog-based regimens.
11q deletions have been found to have more rapid disease progression and poorer survival. Some studies have suggested that when treated with chemotherapeutic agents (e.g., FCR), CLL patients with 11q22 deletion have high rates of response, survival, and relapse-free survival; this suggests that alkylating agents may help overcome to some extent the adverse prognostic effect of del(11q). However, Fink et al observed that presence of del(11q) was still associated with shorter PFS in patients treated with FCR in the CLL8 study.

Other Mutations
Recent advances in next-generation sequencing technology have made it possible to identify other frequently recurring mutations in CLL, among which genetic lesions affecting the NOTCH1, SF3B1, BIRC3, and MYD88 genes are particularly significant. NOTCH1 mutations are found in approximately 8.3% of CLL patients at diagnosis, are usually associated with unmutated IGHV, and are found in higher frequency during disease progression toward Richter’s transformation as well as in chemorefractory CLL. SF3B1 mutations occur in approximately 10% to 20% of patients, tend to occur in CLL with del(11q), and have been associated with a poorer prognosis. BIRC3 mutations have also been associated with a chemorefractory phenotype and tend to have a poor outcome, similar to that of patients with TP53 abnormalities. Taking into account these novel recurrent mutations, Rossi et al have proposed a four-category prognostic model: high risk (patients harboring del(17p)/TP53 mutation and/or BIRC3 mutation), intermediate risk (haboring del(11q), NOTCH1 mutation, and/or SF3B1 mutation), low risk (haboring trisomy 12 or normal karyotype), and very low risk (del(13q) as the sole abnormality). Although these mutations may provide prognostic information to the treating physician, at this time they do not guide initiation of therapy or choice of treatment.

Serum markers
Serum beta-2-microglobulin (β2m) has been found to correlate with clinical stage, marrow lymphocyte infiltration, and bulky disease. High β2m levels are associated with poorer response to frontline standard chemotherapy. In an analysis of the outcomes of 1,674 previously untreated CLL patients who obtained care at MDACC from 1981 to 2004, investigators identified six factors — age, absolute lymphocyte count, sex, β2m, Rai stage, and number of lymph node regions — that correlated with OS. Using these six factors, they developed a nomogram that predicted 5- and 10-year OS better than the clinical staging system. Based on the sum of the points assigned to each of the six factors, a prognostic index score was calculated to stratify untreated CLL patients into three risk groups: low (score 1–3), intermediate (score 4–7), and high risk (score ≥ 8). The estimated median survival times by risk group were: not reached for low risk; 10.3 years (95% CI, 9.5 to 11.0 years) for intermediate risk; and 5.4 years (95% CI, 4.7 to 7.4 years) for high risk. Weaknesses of the study as identified by the authors were inclusion of patients from a single institution and higher proportion of younger patients than the typical CLL cohort (median age was 58 years in the study).

In 2009, Shanafelt et al performed an external validation of the MDACC prognostic index using the CLL database at the Mayo Clinic in Rochester, Minnesota. With a median follow-up of 3.4 years, only age, β2m, number of nodal stations, and Rai stage were found to be independently associated with survival. Following another external validation of the MDACC prognostic index in a multicenter Italian/Swiss CLL population, Bulian et al proposed an alternative prognostic index using age, sex, Binet staging, and β2m. A third validation of the MDACC prognostic index in a multicenter Italian study by Gentile et al indicated that the six prognostic factors proposed by the MDACC remained a significant tool for predicting clinical course in CLL patients.

German Chronic Lymphocytic Leukemia Study Group Prognostic Score
Using data from three prospective randomized phase 3 trials conducted between 1997 and 2006 (CLL trial, CLL4 trial, and CLL8 trial), the German CLL Study Group (GCLLSG) evaluated the prognostic value of 23 clinical, biological, and genetic markers in CLL. Following evaluation of 1,948 eligible CLL patients in the training data set, eight parameters were identified as independent predictors of OS: gender, age, Eastern Cooperative Oncology Group (ECOG) performance status, del(17p), del(11q), IGHV mutational status, serum thymidine kinase, and serum β2m. Total risk score was the sum of the risk scores of the eight individual factors (range, 0–14). The authors proposed four different risk categories for OS: low risk (score 0–2), intermediate risk (score 3–5), high risk (score 6–10), and very high risk (score 11–14). The five-year OS rates ranged from 95.2% (low risk) to 18.7% (very high risk; P < .001). The utility of this prognostic score was later validated.
in an external cohort of 676 newly diagnosed CLL patients at the Mayo Clinic.

**Chronic Lymphocytic Leukemia-International Prognostic Index (CLL-IPI)**

More recently an international initiative to develop a more globally applicable prognostic score has been described as CLL-IPI.57 Data from eight phase 3 CLL trials in France, Germany, the United Kingdom, the United States, and Poland were analyzed to identify five independent variables that predicted for OS: age, clinical stage, del(17p) and/or TP53 mutation, IGHV mutation status, and β2m level. The researchers derived a prognostic index that separated patients into four groups: low (score 0–1), intermediate (score 2–3), high (score 4–6), and very high risk (score 7–10), with significantly different five-year OS of 93%, 79%, 64%, and 23%, respectively ($P < .001$) (Table 1). The reported advantage of the CLL-IPI over previous prognostic indices is that it combines the most important genetic risk factors ($IGHV$ and del(17p)/TP53 mutation) with clinical stage, age, and β2m into an easily applicable prognostic score. This prognostic index is very likely to be used more widely, as it has been validated in multiple countries and is the simplest to use among the prognostic tools.

**Indications for Therapy, with Special Considerations for the Elderly**

Many patients with early-stage CLL do not require therapy and are best managed by observation only. With this approach, patients should be evaluated every three to six months for symptoms and laboratory changes and monitored for the emergence of more active disease. Patients having concerning symptoms or worsening lymphocytosis may require a more extensive workup. Progressive disease should be treated according to the patient’s fitness and comorbidity burden, taking into consideration the presence of high-risk genetic factors.

Standard criteria for initiation of therapy in CLL were initially established by the National Cancer Institute CLL Working Group in 199658 and were updated by the International Workshop on CLL in 2008.13 Based on these criteria, CLL should be treated when there is progressive disease as evidenced by constitutional symptoms due to CLL, symptomatic or massive splenomegaly or lymphadenopathy, progressive marrow failure, rapidly progressive lymphocytosis, or autoimmune cytopenias not responding to steroid therapy (Table 2).

In addition to these standard criteria for treatment initiation, elderly CLL patients should be evaluated individually for comorbidity and/or functional activity prior to initiation of therapy.59-61 A consideration of the social environment and support for the elderly patient may also be an important part of therapeutic decisions.61 Based on data from the CLL4 and CLL5 trials, CLL patients with concomitant diseases who were treated with chlorambucil, fludarabine, or fludarabine plus cyclophosphamide (FC) had a tendency toward inferior survival, independent of age.62 Comorbidities have been postulated to contribute to CLL-unrelated death, facilitate toxicity to CLL treatment, predispose to earlier progression of leukemic disease, and result in a higher rate of CLL-related deaths.61 Elderly patients have a more limited bone marrow reserve vs younger patients.

<table>
<thead>
<tr>
<th>Table 1. — Chronic Lymphocytic Leukemia International Prognostic Index</th>
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<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Genetic abnormality</td>
</tr>
<tr>
<td>Serum β2m</td>
</tr>
<tr>
<td>$IGHV$ mutation status</td>
</tr>
<tr>
<td>Staging</td>
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<td>Age</td>
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$IGHV$ = immunoglobulin heavy chain variable, $β2m$ = beta 2 microglobulin. Low risk = score 0–1, intermediate risk = score 2–3, high risk = score 4–6, very high risk = score 7–10.

<table>
<thead>
<tr>
<th>Table 2. — Standard Indications for Treatment Initiation for Chronic Lymphocytic Leukemia13</th>
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<tbody>
<tr>
<td><strong>At least one of the following criteria should be met:</strong></td>
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<tr>
<td>Evidence of progressive marrow failure as manifested by the development, or worsening, of anemia and/or thrombocytopenia</td>
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<tr>
<td>Massive (&gt; 6 cm below the left costal margin) or progressive or symptomatic splenomegaly</td>
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<tr>
<td>Massive nodes (&gt; 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy</td>
</tr>
<tr>
<td>Progressive lymphocytosis with an increase &gt; 50% over a 2-month period or lymphocyte doubling time (LDT) in $&lt; 6$ months</td>
</tr>
<tr>
<td>Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids or other standard therapy</td>
</tr>
<tr>
<td>Presence of ≥ 1 of the following disease-related symptoms:</td>
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<tr>
<td>• Unintentional weight loss ≥ 10% within the previous 6 months</td>
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<tr>
<td>• Significant fatigue (Eastern Cooperative Oncology Group performance score of ≤ 2; cannot work or unable to perform usual activities)</td>
</tr>
<tr>
<td>• Fevers &gt; 100.5°F or 38.0°C for ≥ 2 weeks without other evidence of infection</td>
</tr>
<tr>
<td>• Night sweats for &gt; 1 month without evidence of infection</td>
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and may recover more slowly from drug-related cytopenias. Since many antileukemic agents are cleared by the kidneys or liver, age-related decline in renal and hepatic function may delay clearance of these medications, thereby necessitating dose reductions.

**Tools for Assessing Comorbidities**

Several tools are available for assessment of comorbidities, functional status, and risk of chemotherapy toxicity for elderly patients with cancer. The cumulative illness rating scale (CIRS) and the Charlson Index correlate closely with each other, and both have been found to be reliable tools for use in trials of older cancer patients, eg, the CLL8 and CLL11 trials. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score is helpful for evaluating risk of hematologic and nonhematologic toxicities from chemotherapy in patients 70 years and older. Using the CIRS, the GCLLSG identified three categories of patients for whom there should be different treatment approaches: “GO GO,” “SLOW GO,” and “NO GO.”

- Medically fit patients with no or minimal comorbidities and normal life expectancy were designated as “GO GO.” Irrespective of chronological age, CLL patients in this category should be considered for intensive chemoimmunotherapy. However, close monitoring of toxicities is still required for elderly patients in this category who are being treated with myelosuppressive agents. Where possible, these patients should be treated in the context of a clinical trial.
- “SLOW GO” patients are less fit and have multiple or severe comorbidities as well as unknown life expectancy. CLL therapy for any patient in this category should be adapted to the patient’s comorbidity burden and individual risk assessment. Clinical trials remain a good treatment option. In the absence of trials, reasonable first-line treatment options for patients in this category are chlorambucil plus obinutuzumab (National Comprehensive Cancer Network [NCCN] category-1 recommendation); ofatumumab plus chlorambucil; chlorambucil plus rituximab; obinutuzumab, rituximab, and chlorambucil monotherapy. Reduced doses of BR or FR are other options that can be considered, especially in the context of a clinical trial. Additional clinical trials and evidence-based therapeutic strategies are still needed for this group of elderly and comorbid CLL patients.
- Patients designated as “NO GO” are frail and have severe comorbidities with very short life expectancy. The risks of antileukemic therapy outweigh the benefits for these patients, and therefore CLL treatment should not be offered except if deemed necessary for palliation of symptoms.

**Management of High-risk CLL in the Elderly Patient**

The presence of high-risk features is not itself an indication to start therapy in any age group. In the elderly population, a more conservative approach may be even more important, to avoid possible toxicities due to therapy initiation.

In physically fit patients without high comorbidity burden and without very high-risk prognostic factors, chemoimmunotherapy with FCR is standard because this regimen has been shown to improve overall survival. Bendamustine plus rituximab (BR) is also a reasonable option for some fit elderly patients with certain comorbid conditions. However, these regimens may not be optimal for patients with higher-risk disease — eg, those with del(17p).

**CLL with del(17p) or TP53 Mutation**

All patients with CLL and del(17p) should be strongly considered for enrollment in a clinical trial. In the absence of a clinical trial, appropriate first-line therapy for this subset of CLL patients includes ibrutinib, high-dose methylprednisolone plus rituximab, alemtuzumab with or without rituximab, or obinutuzumab plus chlorambucil. Patients who show good response to first-line therapy and are fit should be considered for allogeneic stem cell transplantation. Ibrutinib is the only therapy approved for use in patients with del(17p) and is indicated in the NCCN guidelines as a category-1 recommendation for patients age ≥ 70 years and with significant comorbidities and for patients < 70 years who do not have significant comorbidities.

**CLL with del(11q)**

CLL patients with del(11q) should receive an alkylating agent-based regimen as frontline therapy whenever possible. For patients 70 years or older, first-line options include obinutuzumab plus chlorambucil, ofatumumab plus chlorambucil, or bendamustine plus rituximab. In the relapse setting, ibrutinib (NCCN category-1 recommendation) or idelalisib plus rituximab should be considered as the main therapy.

**Important Front-line Chronic Lymphocytic Leukemia Clinical Trials**

Although chemoimmunotherapy regimens (FCR or BR) are excellent treatment options for younger patients with lower-risk CLL, their application in elderly patients is limited by substantial toxicities such as infections and myelosuppression. In the last two decades, several new monoclonal antibodies have been introduced as therapy for many cancers, including CLL. In addition to rituximab, ofatumumab and obinutuzumab now play pivotal roles in the treatment of CLL. Abnormal signaling of the B-cell receptor (BCR) pathway has been linked to the development and main-
tenance of B-cell malignancies, including CLL. This understanding has led to the development of phosphatidylinositol 3 (PI3)-kinase inhibitors (idelalisib) and Bruton’s tyrosine kinase (BTK) inhibitors (ibrutinib) for CLL therapy. The role of chemoimmunotherapy, monoclonal antibodies, and BCR inhibitors in the front-line treatment of elderly CLL patients will be reviewed below.

The international, randomized phase 3 CLL8 trial demonstrated that the addition of rituximab to fludarabine-based chemotherapy improved both PFS and OS compared with fludarabine-only chemotherapy. In this trial, physically fit treatment-naive patients (aged 30 to 81 years, median age 61) with CD20-positive CLL were randomized to six courses of either FC (409 patients) or FCR (408 patients). The investigators reported that FCR was associated with significantly improved response rates vs FC: overall response rate (ORR), 95% vs 88%, and CR, 44% vs 22%, respectively. At three years after randomization, FCR also resulted in higher PFS (65% vs 45%, \( P < .0001 \)). In addition, OS was significantly improved in the patients receiving FCR compared with those receiving FC (87% vs 83%, \( P = .01 \)). FCR was also more frequently associated with grades 3 and 4 neutropenia (3/4 vs 2/1 of patients, \( P < .0001 \)) and leukopenia (24% vs 12%; \( P < .0001 \)).

**Bendamustine Plus Rituximab**

In a German phase 2 trial evaluating the combination of bendamustine plus rituximab (BR) as first-line therapy for CLL, 117 patients aged 34 to 78 years (25.6%, 70 years or older) who had a WHO performance status of 0 to 2 and adequate renal and liver functions were treated with BR every 28 days for up to six courses. ORR was 88.0% (95% CI, 80.7% to 100.0%), with a CR of 23.1% and a PR of 64.9%. After a median follow-up of 27 months, median event-free survival (EFS) was 33.9 months, and 90.5% of patients were alive. Grade 3 or 4 infections occurred in 7.7% of patients, and grade 3 or 4 neutropenia, thrombocytopenia, and anemia were noted in 19.7%, 22.2%, and 19.7% of patients, respectively.

**Ofatumumab**

The monoclonal CD20 antibody ofatumumab binds at a different epitope from the one recognized by rituximab. Ofatumumab has been approved for use in combination with chlorambucil for the frontline treatment of CLL in patient who cannot receive fludarabine-based therapy due to age or comorbidity. The approval of ofatumumab was based on the results of a phase 3 trial in which 447 patients were randomized to receive either ofatumumab plus chlorambucil or chlorambucil alone. Median age was 69 years; 82% of patients were ≥ 65 years, had at least two comorbidities, or both. The primary endpoint of mean PFS was reported as 22.4 months in the ofatumumab plus chlorambucil group vs 13.1 months in the chlorambucil group (hazard ratio = 0.57, \( P < .001 \)). ORR was higher for ofatumumab plus chlorambucil vs chlorambucil (82% vs 69%, \( P = .001 \)), and CR rate was higher (12% vs 1%). After a median follow-up of 29 months, median OS was not reached for either the ofatumumab plus chlorambucil group or the chlorambucil group. Grade ≥ 3 adverse events were experienced by 50% of patients receiving ofatumumab plus chlorambucil and 43% of patients receiving chlorambucil alone, with the most common adverse event being neutropenia. Grade ≥ 3 infections were reported in 15% and 14% of ofatumumab plus chlorambucil and chlorambucil-alone patients, respectively.

**Obinutuzumab**

Obinutuzumab is a humanized monoclonal antibody against CD20 whose binding properties differ from agents like rituximab and ofatumumab. Compared with rituximab and ofatumumab, obinutuzumab demonstrated elevated antibody-dependent cytotoxicity and markedly higher induction of lysosome-mediated cell death. The open-label, multicenter, three-arm CLL11 trial investigated the safety and efficacy of obinutuzumab plus chlorambucil vs rituximab plus chlorambucil or chlorambucil alone in previously untreated CLL patients with comorbidities. In this study, 781 CLL patients with median age of 73 years, creatinine clearance of 62 mL/minute, and baseline CIRS score of 8 were randomized to one of the three treatment arms. Treatment with obinutuzumab plus chlorambucil, rituximab plus chlorambucil, or chlorambucil monotherapy resulted in median PFS of 26.7 months, 16.3 months, and 11.1 months, respectively. OS was also prolonged by treatment with obinutuzumab plus chlorambucil compared with chlorambucil alone (hazard ratio for death, 0.41; 95% CI, 0.23 to 0.74; \( P = .002 \)). In the obinutuzumab plus chlorambucil group, grade 3 or 4 infusion-related reactions occurred in 20% of patients during the first infusion of obinutuzumab, but there were no grade 3 or 4 reactions during subsequent infusions. Rates of grade 3 to 5 infection were 11% to 14% but did not differ significantly among the treatment groups. In combination with chlorambucil, obinutuzumab is now approved for frontline treatment of CLL, and the combination is recommended by the NCCN guidelines as a category-1 treatment of choice for older patients with comorbidities.

**Ibrutinib**

The safety and activity of ibrutinib, an oral BTK inhibitor, in treatment-naive CLL patients aged 65 years and older were initially assessed in an open-label phase Ib/2 trial. Twenty-nine patients with CLL and two patients with SLL (median age, 71 years; range, 65 to 84 years) were treated with 28-day cycles of once-daily...
Ibrutinib 420 mg. After a median follow-up of 22.1 months, 22 patients (71%) achieved an objective response (95% CI, 52.0 to 85.8); four patients (13%) had a CR; one patient (3%) had a nodular partial response; and 17 (55%) patients had a PR. An additional four patients (13%) achieved PR with lymphocytosis, resulting in an ORR of 84%. Median time to response was 1.9 months. Toxicities included diarrhea, nausea, and fatigue and were mostly of mild-to-moderate severity (grades 1–2). Three (10%) patients developed grade 3 infections, one patient developed grade 3 neutropenia, and one patient developed grade 4 thrombocytopenia. Ibrutinib can cause increased lymphocytosis, which should not be mistaken for disease progression in the early phases of therapy. With three years of follow-up, 81% of treatment-naive patients continued on ibrutinib, and there were no relapses for more than two years. At a median treatment duration of 30 months, the ORR was 84%, with 23% attaining CR, 55% PR, and 6% PR with lymphocytosis. The estimated 30-month PFS rate was 96%, and the estimated 30-month OS was 97%. The most common grade 3 or higher adverse events over the three years of follow-up were hypertension (23%), pneumonia (6%), neutropenia (3%), and thrombocytopenia (3%).

**Idelalisib**

Idelalisib, a selective oral inhibitor of PI3K-delta, is licensed for use in combination with rituximab as treatment for patients who previously received at least one line of therapy. The activity of idelalisib has been evaluated for use in elderly patients in several studies. As proposed by Cheson et al,75 patients who are being treated with idelalisib or ibrutinib and who have shown some clinical response in meeting the PR criteria but who have persistent lymphocytosis should receive PR status.

Response Assessment and Goals of Therapy for Elderly Chronic Lymphocytic Leukemia Patients

Following treatment for CLL, patients can be classified as having CR, partial remission (PR), stable disease, progressive disease (PD), or refractory disease.13 As proposed by Cheson et al,75 patients who are being treated with idelalisib or ibrutinib and who have shown some clinical response in meeting the PR criteria but who have persistent lymphocytosis should receive PR status.

Treatment goals in elderly CLL patients should aim for symptom control and improvement of quality of life rather than for induction of high CR rates. Because aggressive therapy is typically not well tolerated in these patients, strong consideration should be given to health-related quality of life issues when choosing a treatment regimen.

Even when choosing to treat with BCR inhibitors (ibrutinib and idelalisib), the treating physician must remember that, although these medications may not be as myelosuppressive as chemotherapy, they are associated with chronic adverse events. Among the most common important adverse events reported in studies were low-grade bleeding, diarrhea, atrial fibrillation, and rash (with ibrutinib) and hepatotoxicity, colitis, intestinal perforation, pneumonitis, and rash (with idelalisib), and patients should be evaluated frequently for these.
Conclusion
CLL is the most prevalent leukemia in the Western world. It is also predominantly a disease of the elderly, with a median age of 72 years at diagnosis. Many patients are asymptomatic and may not require therapy for many years. Others have certain disease characteristics that confer higher risk of progression and therefore require therapy soon after diagnosis. Chemomunotherapy with FCR is the standard choice for younger CLL patients who are physically fit. Many elderly patients cannot tolerate intensive regimens and need individualized therapy based on their comorbidities and functional status. Where indicated, certain elderly CLL patients — ie, those who are frail or have significant comorbidities — are better served by receiving no treatment at all. Irrespective of the treatment option chosen for any particular elderly patient, clinicians should consider quality of life issues as well as the need to manage acute and chronic adverse effects of medications. Enrollment in appropriate clinical trials remains the optimal frontline treatment choice for all elderly CLL patients.

References


Advances in knowledge of pathogenesis and availability of novel therapies can improve the management of chronic lymphocytic leukemia, particularly in the elderly.

Management of Chronic Lymphocytic Leukemia in the Elderly
Jacqueline C. Barrientos, MD

Background: Because chronic lymphocytic leukemia (CLL) typically follows an indolent course, many patients do not need to initiate therapy until they reach a relatively advanced age, when frailty and reduced organ function can make some of the standard treatments difficult to tolerate and less effective. However, recent advances in the understanding of CLL biology and the approval of agents in novel treatment classes have offered significant advances in the management of the disease.

Methods: The author reviewed current treatment goals in CLL management, including issues surrounding complete remission (CR) and minimal residual disease (MRD); the findings of trials of treatments from novel drug classes, primarily kinase inhibitors and monoclonal antibodies; and current strategies for use of standard and novel therapies for treatment of individuals diagnosed with CLL, particularly elderly patients.

Results: Several agents and regimens featuring improved clinical outcomes and tolerability are now available or in advanced development for the management of CLL patients, including the elderly and those with high-risk disease. These include ibrutinib, idelalisib plus rituximab, and obinutuzumab plus chlorambucil.

Conclusion: The availability of Bruton’s tyrosine kinase inhibitors and phosphatidylinositol 3-kinase inhibitors and other novel therapies will allow elderly CLL patients to receive more efficacious treatment with greater tolerability than available with traditional approaches for management of the disease.

Introduction
Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia in the Western world, accounting for approximately 30% of all leukemias diagnosed in the United States. Approximately 14,600 new cases of CLL are expected to be diagnosed in the United States in 2015.1 CLL primarily affects the elderly, with the majority of patients being > 65 years of age at diagnosis.2 Following diagnosis, most patients are monitored through a “watch and wait” approach, and therapy typically is not initiated until symptoms develop. Manifestations of CLL include fevers, night sweats, weight loss, symptomatic lymphadenopathy, or bone marrow failure (as evidenced by worsening anemia or thrombocytopenia).3 By the time most patients require therapy, the majority have multiple chronic comorbidities, in-
cluding hypertension, arrhythmias, renal insufficiency, or other conditions that limit their quality of life and performance status. Therefore, patients typically receive their first therapy at an age when they may be too frail to tolerate a regimen that may be associated with severe toxicities.

Over the last decade, the understanding of CLL biology has advanced considerably with the discovery of chromosomal abnormalities and genetic mutations that contribute to the heterogeneity of the disorder and help predict its clinical course. Similarly, the discovery of the role of the microenvironment and of the signaling factors that play a key role in CLL pathogenesis has advanced clinicians’ understanding of the condition and has led to the development of agents that specifically target dysregulated pathways. With the approval of several new targeted agents having unprecedented clinical activity (particularly in patients with high-risk disease, poor prognostic markers, and inability to tolerate cytotoxic chemotherapy regimens), a transformation is occurring in the treatment of patients with a CLL diagnosis.

Because of the aging of the population and increased life expectancy of the elderly, CLL will likely become a progressively more common cause of morbidity and mortality in older individuals. The goal of this review is to describe novel treatment approaches by highlighting agents recently approved by the US Food and Drug Administration (FDA) that will impact the management of CLL, particularly in the frail and the elderly.

**Principles of Chronic Lymphocytic Leukemia Treatment**

**Prognostic Factors**

The clinical course of CLL is heterogeneous, hence the need for staging and prognostic assessment to determine the anticipated disease course. The prognosis of CLL is affected by disease stage, the patient’s cytogenetic and molecular profile, and the patient’s functional ability to tolerate therapy. There is no evidence that initiation of therapy for asymptomatic early-stage disease (Rai 0–2 or Binet A) improves survival. Outside of clinical trials, treatment of early disease is recommended only if a patient develops B symptoms (fever, night sweats, unintentional weight loss) or disease progression (e.g., worsening lymphadenopathy or bone marrow failure).

Unfavorable genomic and molecular features include the presence of unmutated immunoglobulin heavy chain variable (IGHV) gene, CD38 overexpression, zeta-chain-associated protein kinase (ZAP)-70, and specific chromosomal aberrations, including 11q deletion, 17p deletion, and the presence of a TP53 mutation. A patient’s molecular profile affects treatment decisions: for patients with evidence of a 17p deletion and/or a TP53 mutation, the treatment options are limited. The only FDA-approved agent to treat a 17p deletion CLL patient, regardless of previous therapy, is the Bruton’s tyrosine kinase (BTK) inhibitor ibrutinib, although other agents have shown clinical activity in this patient population, including the monoclonal antibody alemtuzumab and the phosphatidylinositol 3-kinase delta (PI3Kδ) inhibitor idelalisib.

**Treatment Approaches**

Although early intervention is considered crucial in most malignant diseases, this is not the case in CLL. The lack of evidence that CLL can be cured with currently available modalities has resulted in a “watch and wait” approach for most patients. Except for allogeneic bone marrow transplant, which is not an option in the majority of individuals aged 70 years and older, current treatment approaches are not curative. The treatment of asymptomatic early-stage disease is not indicated even in the presence of high-risk disease (such as a 17p deletion or TP53 mutation). The addition of immunotherapy to combination regimens of cytotoxic chemotherapy has demonstrated superior response and survival. Indeed, because of treatment advances over the past few decades, CLL patients’ median survival from the time of diagnosis has increased from 96 months in 1980 to > 120 months in 2002.

Although several treatments are available for CLL, the duration of response and of progression-free survival (PFS) decreases and the risk of complications increases with every successive line of treatment (Fig). Therefore, practitioners should employ their clinical judgment in making treatment decisions, with the goal of achieving the most durable remission possible with the initial therapy, especially in older individuals, who are more susceptible to treatment complications and may not tolerate a second treatment regimen.

A remaining area of treatment controversy is whether minimal residual disease (MRD) should be pursued in addition to a clinical complete remission (CR). MRD is defined as < 0.1% of leukemic lympho-
cytes in the bone marrow detected by oligonucleotide polymerase chain reaction (PCR) and four-color flow cytometry. The absence of MRD after fludarabine-based chemoimmunotherapy is associated with a more prolonged PFS and overall survival (OS), although outcomes in the setting of novel targeted agents have not yet been established. The duration of response while using a novel targeted agent may not necessarily correlate with the depth of response, and a remission may not be necessary to obtain durable clinical benefit for as long as continuous therapy is offered.

Whereas in younger or fit patients the aim may be to achieve a CR and MRD negativity with the use of chemoimmunotherapy, this approach traditionally has been poorly tolerated in patients with multiple comorbidities. For elderly individuals, early detection of absence of MRD may prompt early chemoimmunotherapy cessation, thereby substantially reducing the risk of treatment-related toxicity. Alternatively, frail patients may benefit primarily from a low-intensity approach in which the therapeutic endpoint is not CR or MRD, but rather duration of remission, tolerability, and quality of life. There is a clear need for greater representation of elderly and frail patients in randomized CLL clinical trials to assess the therapeutic goals of CR and MRD negativity in this patient population, particularly in the era of kinase inhibitor therapy. MRD negativity should be regarded as a treatment goal only in the setting of a clinical trial.

**Medications**

Table 1 contains a list of the most common medications utilized in the treatment of CLL. Outlined here are targeted and immune-directed therapies that are impacting the way clinicians treat CLL.

The current CLL treatment paradigm is evolving based on the understanding of the disease’s pathophysiology. The B-cell receptor (BCR) regulates fundamental proliferation and survival mechanisms for malignant B-cells. These functions are mediated by signals that are transmitted intracellularly downstream through several kinases, including Lyn kinase, spleen tyrosine kinase (SYK), PI3K, BTK, and others. Targeting these kinases, in particular the BTK and the PI3K signaling pathways, has shown remarkable clinical activity in patients with CLL and with other B-cell malignancies.7,18

**Ibrutinib:** BTK is a cytoplasmic tyrosine kinase involved in signaling of the BCR and chemokine receptors. Ibrutinib is the first-in-class oral agent targeting the BTK pathway by forming a covalent bond with its active site, cysteine-481. It achieves target inhibition with once-daily oral dosing. In vitro and in vivo models demonstrate that ibrutinib inhibits survival, proliferation, and migration of CLL cells.18 Ibrutinib inhibits secretion of CCL3 and CCL4 by CLL cells, and at least part of this process occurs in a BCR-dependent manner.19 Use of ibrutinib (or any agent targeting the B-cell receptor pathway) results in rapid lymphocytosis accompanied by a marked reduction in lymphadenopathy, a “redistribution” phenomenon that is reversible upon temporary discontinuation of the targeted agent.18 In a phase 1b/2 clinical trial, treatment with ibrutinib monotherapy in patients with relapsed or refractory CLL resulted in an overall response rate (ORR) of 71% and durable remissions (estimated PFS at 26 months: 75%) for all patient groups, including elderly patients and those with high-risk disease.20 In the phase 3 RESONATE trial for patients with relapsed or refractory CLL, ibrutinib was evaluated against ofatumumab. Ibrutinib demonstrated improved PFS and OS vs ofatumumab, with outcomes independent of 17p deletion status.21 Minimal toxicities reported with ibrutinib included diarrhea, grades 1 and 2 pyrexia and infections, and grades 1 and 2 bleeding events.

**Idelalisib:** Idelalisib is a first-in-class inhibitor of PI3K, which plays a pivotal role in signal transduction involved in the growth, proliferation, differentiation, and survival of B-cells. A randomized, double-blind, placebo-controlled phase 3 trial of rituximab with or without idelalisib in CLL patients was discontinued.
early on the recommendation of an independent data and safety monitoring board after the combination regimen demonstrated clear superiority vs the monotherapy arm. The reported ORR was 81% in patients receiving idelalisib plus rituximab vs 13% in patients receiving rituximab plus placebo.\textsuperscript{22} The most common adverse events associated with idelalisib included pyrexia, fatigue, and nausea. It is important to note that, although the drug was initially well tolerated, a severe noninfectious secretory diarrhea (grade 3 or 4) and/or colitis was reported as a late toxicity in 14% of study participants.\textsuperscript{25}

Both ibrutinib and idelalisib have shown clinical activity in deletion 17p and/or in TP53-mutated disease.\textsuperscript{10,13} Because of their excellent tolerability and effectiveness, both ibrutinib and idelalisib appear particularly suitable for the treatment of elderly individuals. Ongoing trials are evaluating these drugs’ usefulness both alone and in various combinations as frontline CLL treatment in frail and elderly patients.\textsuperscript{24,25}

**Obinutuzumab:** Rituximab, ofatumumab, and obinutuzumab are monoclonal antibodies directed at the CD20 antigen and are used mainly in combination with other chemotherapeutic agents. Except for the possibility of severe or life-threatening infusion reactions and viral hepatitis reactivation, these agents are generally well tolerated. The most promising of these monoclonal antibodies that target CD20 is obinutuzumab. Obinutuzumab differs from previous anti-CD20 monoclonal antibodies with respect to its glyco-engineered crystallizable fragment (Fc) region and its type 2 CD20-binding mode. Glyco-engineering increases the binding affinity of the Fc portion of obinutuzumab to the Fcγ receptor III on innate immune effector cells (such as neutrophils, natural killer cells, and macrophages); in turn, this results in improved antibody-dependent cell-mediated cytotoxicity and antibody-dependent cellular phagocytosis.\textsuperscript{26} Obinutuzumab is indicated in combination with chlorambucil for use in treatment-naive CLL patients, based on the findings of a large phase 3 trial in which treatment-naive patients were randomized to receive either chlorambucil or chlorambucil plus rituximab or chlorambucil plus obinutuzumab.\textsuperscript{27} In elderly (median age 73 years) patients with multiple debilitating comorbidities, the combination of obinutuzumab with chlorambucil was associated with a significant and clinically meaningful prolongation of PFS, increased CR, and an increased rate of MRD negativity, compared with the results obtained with the rituximab plus chlorambucil combination. Moreover, treatment with obinutuzumab plus chlorambucil resulted in a significant OS benefit compared with chlorambucil monotherapy, suggesting that the induction of deeper remissions (ie, MRD negativity) could translate into a survival advantage even in frail patients.\textsuperscript{26} Combination studies of obinutuzumab with the novel inhibitors of B-cell receptors are planned.

**Alemtuzumab:** Alemtuzumab is a monoclonal antibody directed against the CD52 antigen and is approved for use as monotherapy in CLL. Data from clinical trials suggest that the drug has good clinical activity in patients with minimal nodal disease and in those with 17p or 11q deletions. Until the introduction of ibrutinib, alemtuzumab was the most commonly used agent in patients with 17p deletion or TP53-mutated disease.\textsuperscript{11,12} Alemtuzumab may still represent an option for patients whose CLL has failed to respond to other treatments. Alemtuzumab can have substantial toxicity, including fevers, pancytopenia, and severe viral or fungal infections, particularly reactivation of cytomegalovirus. Concerns about its infectious complications contributed to its limited use in CLL patients. The drug was withdrawn from the US and European markets, but it is still available through manufacturer-sponsored patient access programs.

**Lenalidomide:** Although not FDA-approved, lenalidomide is another targeted agent that has shown promising clinical activity in CLL patients.\textsuperscript{28,29} Unfortunately, the frontline study evaluating lenalidomide vs chlorambucil in CLL patients older than 65 years (ORIGIN trial, NCT00910910) had to be halted due to safety concerns. The patients randomized to lenalidomide had a 92% increased risk for death compared with the patients receiving chlorambucil. Adverse effects of lenalidomide use include neuropathy, thrombocytopenia, and thrombotic events. At this time, the role of lenalidomide in the management of CLL is not well defined because of the availability of multiple other treatment options.

**Treatment Strategies**

Current recommended initial treatment of CLL includes a combination of cytotoxic chemotherapy plus a CD20 monoclonal antibody in young patients or fit elderly patients. The most common regimens are (1) fludarabine, cyclophosphamide, and rituximab (FCR) and (2) bendamustine plus rituximab (BR). Recently, a large European phase 3 trial demonstrated the PFS superiority of FCR vs BR in patients with unmutated IGHV.\textsuperscript{30} In addition, FCR was associated with increased rates of complete remission and MRD negativity; in the setting of chemoimmunotherapy, this finding correlates with longer remission duration and possibly survival. The investigators recommended that, in fit patients without 17p deletion or TP53 mutation, FCR should be the preferred frontline treatment. It is important to note that the median age of the patients in both arms was 61 years, which is a decade younger than the median age at CLL diagnosis and the patients that participated in the trials were fit with few comorbidities. The difference in PFS was not statistically significant.
between the arms in patients ≥ 65 years old, suggesting that fit elderly patients may benefit from treatment with BR rather than FCR. FCR use was associated with increased risk of neutropenia, febrile neutropenia, and other complications that may be particularly severe and potentially lethal in older individuals (treatment-related mortality: 3.9% [FCR] vs 2.1% [BR]).

Despite the availability of combination regimens like FCR and BR, until very recently the frontline management of older and unfit CLL patients had been limited to the use of chlorambucil or rituximab monotherapy. The use of chemoimmunotherapy regimens was not an option until the recent report by Goede et al.27 The pivotal phase 3 study demonstrated the superiority of the combination of chlorambucil plus obinutuzumab against chlorambucil alone in terms of PFS, CR, and OS. This registrational trial did not include age as an eligibility criterion; rather, it used the presence of a high cumulative illness rating scale (CIRS) score, which describes functional comorbidity and/or the presence of impaired renal function (patients of any age with a glomerular filtration rate of 30 mL to 69 mL/min). This study represents a major advance in the treatment of elderly patients with CLL who lack a 17p deletion and establishes a standard of care for the elderly and for frail patients with multiple medical conditions.

In another important phase 3 study evaluating the use of chemoimmunotherapy in elderly patients (median age 69 years) with multiple comorbidities, Hillmen et al33 compared chlorambucil in combination with the anti-CD20 monoclonal antibody ofatumumab vs chlorambucil alone in patients for whom fludarabine therapy was inappropriate based on age or comorbidities. Patients receiving the combination treatment experienced a substantial improvement in PFS.

The only agent currently approved for use in patients with a 17p deletion is ibrutinib. Although idelalisib (in combination with rituximab) has not been approved for this particular indication, clinical trials have shown clinical activity in patients with a 17p deletion,13 and this would be a reasonable treatment approach in patients unable to tolerate ibrutinib therapy. For eligible patients, evaluation for allogeneic bone marrow transplantation is recommended in any patient with high-risk disease. Clinicians should make a decision only after carefully deliberating the advantages and disadvantages of continued therapy vs stem cell transplant. Conditions potentially favoring transplant include younger age and availability of a donor for a high-risk-disease patient carrying the 17p deletion or 11q deletion.32 The longest follow-up data of ibrutinib-treated patients having a 17p deletion (with a median of four prior therapies) reported a median PFS of 28 months. It is important to recognize that PFS with ibrutinib varies by interphase cytogenetic abnormality, with 17p deletion patients having a 30-month estimated PFS rate of 48% (less than the 74% rate observed for 11q deletion patients and the 87% rate observed when neither of these genomic aberrations is present).33 More recent data suggest that complex karyotype may also be a risk factor.34,35 In fact, most patients with relapsed or refractory CLL who discontinued ibrutinib early were difficult to treat and had poor outcomes with relatively short survival.33,34 Published data regarding the sequencing of these new agents are relatively limited and anecdotal. Until greater clarity develops regarding which newer agents can be recommended as salvage therapy in patients whose disease progressed following ibrutinib therapy, transplantation will remain an important consideration for fit, transplant-eligible patients with a deletion 17p (or other high-risk characteristic), as transplant offers a potentially curative therapy.

For previously treated patients, ibrutinib as a single agent proved significantly more effective than ofatumumab in the open-label phase 3 RESONATE study in CLL patients with measurable nodal disease who were not eligible for treatment with purine analog-based therapy and who had received ≥ 1 prior therapies.21 The outcomes of the 391 patients (median age 67 years) with relapsed CLL who participated in this trial were recently updated. The ORR with ibrutinib was 90% vs 25% with ofatumumab; PFS was not reached at 15 months with ibrutinib and was reached at 8.1 months with ofatumumab.36 With longer follow-up, ibrutinib-treated patients maintained the improved OS. No significant difference in 12-month PFS was observed in ibrutinib-treated patients with or without 17p deletion or for those who developed lymphocytosis compared with those without lymphocytosis. These dramatic results, which did not appear to be influenced by patient age and were achieved with minimal toxicity, have established ibrutinib as the preferred second-line agent in CLL.

In another pivotal phase 3 study in patients ineligible for cytotoxic therapy, the combination of idelalisib plus rituximab proved superior to rituximab alone in relapsed CLL. Of the 220 patients enrolled, 78% were 65 years and older.22 The median PFS duration was 5.5 months for rituximab and > 15 months for idelalisib plus rituximab; OS was also greater with combination therapy (92% in the idelalisib plus rituximab group vs 80% in the rituximab plus placebo group at 12 months). The results were independent of patient age or 17p deletion.13 The combination of idelalisib plus rituximab was well tolerated; adverse events reported included diarrhea, grades 1 and 2 pyrexia and infections, and grades 1 and 2 transaminitis.

As described, a number of new therapeutic options are available in the frontline and second-line (or beyond) settings for CLL patients (Table 2). These novel agents are associated with prolonged survival in CLL.
patients, including those with high-risk disease who historically have had poor survival rates. These targeted therapies are particularly promising for patients 70 years and older, whose numbers will progressively increase and who already represent the largest cohort of CLL patients.

Management of Older Individuals with Chronic Lymphocytic Leukemia

Based on the findings reviewed in this article, this author proposes that older CLL patients or patients with comorbidities should be considered for participation in a clinical trial if available or treated according to the therapy recommendations outlined in Tables 2 and 3. All individuals 70 years of age and older should undergo a comprehensive geriatric assessment before initiation of therapy to estimate cancer-independent mortality risk and tolerance of chemotherapy and to identify conditions that may interfere with the treatment. These may include the potential for drug-drug interactions due to polypharmacy, poor access to nutrition, inadequate social support, depression, memory disorders, and other coexisting illnesses or conditions that may necessitate interventions, as these may affect the therapeutic effect of the proposed treatment plan. It is very important to individualize the patient’s therapy based on the specific clinical presentation.

In the near future, novel agents such as those discussed in this article may be shown to have comparable or even improved outcomes with greater tolerability compared with FCR. Two large cooperative group trials in the United States are currently evaluating whether the rational use of targeted agents such as ibrutinib in the frontline setting is superior in terms of duration of remission, survival, quality of life, and tolerability in fit patients up to the age of 70 years (FCR vs ibrutinib plus rituximab [NCT02048813]) and in older patients with comorbidities (BR vs ibrutinib vs ibrutinib plus rituximab [NCT01886872]). Several other ongoing clinical trials are specifically accruing patients older than 65 years with the goal of improving current outcomes (more information can be obtained at www.clinicaltrials.gov).

Most importantly, in addition to the recently approved agents, an array of promising new therapeutic interventions are undergoing evaluation in clini-
clinical trials, including second-generation BTK or PI3Kδ inhibitors, anti-apoptotic inhibitors, targeted tumor-specific cellular therapies, and others. The rational design of targeted agents appears to address elderly patients’ unmet needs with respect to improved efficacy and tolerability. With the introduction of these agents into the CLL armamentarium, clinicians may be able to exploit combination strategies that enable patients to achieve longer remissions, potentially altering the natural course of the disease. In fact, it may be possible to envision a future in which patients can receive chemotherapy-free treatment that is potentially curative.

References
30. Eichhorst B, Fink AM, Busch R, et al. Frontline chemo-immunotherapy with fludarabine (F), cyclophosphamide (C) and rituximab (R) (FCR) shows superior efficacy in comparison of bendamustine and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): Final analysis of the German CLL study group (GCLLSG) (CLL10 study). Program and abstracts of the 56th ASH Annual Meeting and Exposition; December 6-9, 2014; San Francisco, California. Abstract 19.
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