Optimizing Treatment of Chronic Lymphocytic Leukemia

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Presenter's disclosure of conflicts of interest is found at the end of this article.

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Abstract

During JADPRO Live Virtual 2020, Sandra Kurtin, PhD, ANP-C, AOCN®, described personalization of the treatment of chronic lymphocytic leukemia (CLL) using molecular attributes of the disease, as well as patient characteristics. Dr. Kurtin discussed front-line treatment in previously untreated patients, treatment for relapsed or refractory CLL, and how to prevent, mitigate, and manage adverse events in order to optimize treatment.

Treatment of chronic lymphocytic leukemia (CLL) is becoming increasingly personalized, relying on both the molecular attributes of the disease and patient characteristics.

During JADPRO Live Virtual 2020, Sandra Kurtin, PhD, ANP-C, AOCN®, of the University of Arizona Cancer Center, identified key factors to consider when selecting treatment for patients with CLL, applying current guidelines to front-line treatment and treatment of relapsed/refractory disease. Dr. Kurtin also described the advanced practitioner's role in the prevention, mitigation, and management of adverse events.

PERSONALIZING TREATMENT

Some of the basic principles for personalizing treatment include disease attributes and patient symptoms. All lymphoid malignancies have variability in how they present, said Dr. Kurtin, based on disease burden and whether the disease is primarily nodal or in the bone marrow and blood. The genetic risk of CLL also guides treatment and prognosis as does the fitness and concomitant diseases of the patient. Finally, the treatment situation itself—line of therapy, response and duration of response to prior treatment, adverse events, and patient preferences—plays a major role in optimizing treatment (Hellek, 2019).

The two most common staging criteria for CLL are the Rai and the Binet staging systems. They were both developed utilizing clinical parameters of disease and were the cornerstone of prognostic decision-making until more recent molecular markers became available.

"These two staging systems are simple, inexpensive, and rely solely on a physical examination and stan-

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dard laboratory tests," said Dr. Kurtin. "Additional molecular factors are considered in the risk stratification of the disease."

The stage of disease sets some level of prognostic indication, but more recently, providers have looked at the CLL international prognostic index, which incorporates fluorescence in situ hybridization (FISH) testing results among other factors. FISH can detect the presence or absence of deletion 17p or *TP53* mutation. Patients who carry this marker have an inferior prognosis compared with other patients with CLL, said Dr. Kurtin.

GENOMIC ALTERATIONS IN CLL

According to Dr. Kurtin, the presentation and clinical course of CLL is highly variable (Table 1). Chronic lymphocytic leukemia can present as an aggressive and life-threatening leukemia or as an indolent form that will not require treatment over decades. While the currently available clinical staging systems for CLL are simple and inexpensive, said Dr. Kurtin, they lack accuracy to predict disease progression and survival on an individual basis. The increased understanding of molecular pathogenesis has provided improved understanding of biological factors that correlate with clinical outcomes in CLL.

"Patients who have only a 13q deletion, for example, may never require therapy," said Dr. Kurtin, who noted that the median treatment-free survival with that mutation is 7.6 years. "A lot of people do very well when that is their sole abnormality."

Patients with a 17p deletion, on the other hand, have a median treatment-free survival of only 9 months. However, the size of the clone is an important prognostic factor (Cramer & Hallek, 2010). A very small 17p clone may not behave as aggressively, while a larger clone is associated with inferior survival. Patients with a larger clone will be considered for earlier treatment using therapies known to have a benefit in the presence of 17p, said Dr. Kurtin (Table 2).

In addition to the risk level of the disease, providers also look to the Cumulative Illness Rating Scale, which has been widely used in clinical trials (Kurtin, 2017). Patients who are fitter are considered for more robust treatment. Patients who are vulnerable or unfit require treatment tailored specifically to their level of fitness and personal goals for treatment. For terminally ill patients, on the other hand, the focus is supportive care.

PATHWAYS AND TARGETS IN CLL

As Dr. Kurtin explained, there is very little role for standard chemotherapy in the treatment of CLL. Rather, the focus is largely on actionable targets, including CD20, CD52, BTK, PI3K, and BCL2.

Monoclonal Antibodies

Rituximab (Rituxan), a chimeric monoclonal antibody that targets the protein CD20, has long been approved for CLL. More recently, anti-CD20 antibodies ofatumumab (Kesimpta) and obinutuzumab (Gazyva) have been used to treat recurrent or progressive disease.

"There has been significant improvement in overall survival over time for patients receiving chemoimmunotherapy with an anti-CD20 monoclonal antibody compared to patients without chemoimmunotherapy," said Dr. Kurtin. "This has made a huge difference in what we expect and how we optimize treatment for CLL."

In addition, alemtuzumab (Lemtrada) has seen a resurgence in selective cases targeting CD52, and chimeric antigen receptor (CAR)-T clinical trials targeting CD19 in CLL have demonstrated improved outcomes.

Table 1. Genomic Alterations in CLL

Alteration	Risk (with sole abnormality)	Median survival	Median TFS
13q deletion	Favorable	133 mo (11 yr)	92 mo (7.6 yr)
Normal	Neutral	111 mo (9.25 yr)	49 mo (4.1 yr)
Trisomy 12	Neutral	114 mo (9.5 yr)	33 mo (2.75 yr)
11q deletion	Unfavorable	79 mo (6.5 yr)	13 mo
17p deletion	Unfavorable	32 mo (2.6 yr)	9 mo

Note. TFS = treatment-free survival. Information from Cramer & Hallek (2010).

Table 2. Indications for Therapy Include the Extent and Severity of Disease Manifestations

Category	Reasons for treatment
CLL-related symptoms	• Significant B symptoms (e.g., night sweats, fever without infection, severe fatigue, unintentional weight loss)
Tumor burden	• Massive nodes (i.e., 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy • Massive (i.e., 6 cm below the left costal margin) or progressive or symptomatic splenomegaly • Progressive lymphocytosis with an increase of > 50% over a 2-mo period • Lymphocyte doubling time < 6 mo (if ALC > 30×10^9/L) • Threatened end-organ function (e.g., enlarged lymph node obstructing bowel) • Richter's transformation
Bone marrow failure	• Progressive anemia (Hgb < 11 mg/dL) • Progressive thrombocytopenia (Plt < 100,000)
Immune dysfunction	• Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids or other standard therapy

Note. ALC = absolute lymphocyte count. Information from Hallek (2015); Hallek et al. (2018).

The most common adverse events associated with monoclonal antibodies are infusion-related reactions. Most of these reactions occur in the first cycle of treatment, in patients with bulky disease, and often within the first few minutes of therapy. Although true anaphylaxis is rare, said Dr. Kurtin, it's possible in previously exposed individuals. Infusion-related reactions are managed with premedication: H_1, H_2, steroids, and acetaminophen. There should be standing orders in place for immediate management, said Dr. Kurtin. Although very rare, mucocutaneous reactions can also occur and may be severe in some patients. These can cause bloating, diarrhea, abdominal pain, and even nausea and emesis and may require treatment with steroids.

Patients on monoclonal antibodies are also at risk for infection. "These agent are targeting B lymphocytes, which is our humoral immunity, so you can see some immunosuppression over time," said Dr. Kurtin, who noted that antibodies "tend to stick around for a while."

BTK Inhibitors

Bruton's tyrosine kinase or BTK is part of the BCR signaling pathway, which is involved in B-cell proliferation, differentiation and survival. It's also involved in B-cell trafficking and tissue homing via interactions with the tissue microenvironment. As BTK inhibition leads to the disruption of BCR signaling and B-cell apoptosis, homing and migration patterns largely explain the common pattern of rapid reduction in lymphadenopathy and an increase in lymphocytosis. According to Dr. Kurtin, this phenomenon is typically resolved within the first 6 months of treatment, and it's important not to confuse it with progression of disease.

BTK inhibitors also have some unique toxicities. One of the concerns with BTK inhibitors is hemorrhage, as fatal bleeding events have occurred. Providers should also be mindful of people who need anticoagulation or antiplatelet therapy for CLL. Patients with atrial fibrillation or other heart abnormalities or a history of clotting should be monitored very carefully, said Dr. Kurtin.

Patients who are on BTK inhibitors are also at an increased risk for acquiring an infection, including rare infections such as progressive multifocal leukoencephalopathy and *Pneumocystis jiroveci* pneumonia.

Patients with new onset of atrial fibrillation, the most common dysrhythmia, can continue treatment, but should be monitored closely and comanaged with a cardiologist. Secondary primary malignancies, mostly skin cancers, can also occur, said Dr. Kurtin.

BCL2 Inhibitors

Proteins in the B-cell CLL/lymphoma 2 (BCL-2) family are key regulators of the apoptotic process. Venetoclax (Venclexta) induces p53-independent apoptosis of CLL cells and was approved by the FDA for treatment of adult patients with CLL or small lymphocytic lymphoma (Kurtin & McBride, 2017).

The increase in cell death, however, puts patients with bulky disease who have a high white blood cell count at risk of developing tumor lysis. Concomitant use of strong CYP3A inhibitors at initiation and during ramp-up phase is thus contraindicated due to the potential for increased risk of tumor lysis syndrome. Patients on a BCL2 inhibitor are also at risk of infection, and fatal infections like pneumonia and sepsis have occurred. Finally, venetoclax requires dose adjustment for hepatic impairment.

PI3K Inhibitors

PI3Ks mediate signals from the B-cell receptor, facilitate the development of functional B cells, and support the growth and survival of neoplastic B cells, including CLL cells. Inhibition of PI3K directly affects stromal elements including vasculature (angiogenesis), infiltrating immune cells, fibroblasts, and connective tissue, which disrupts the normal nurturing processes needed for cellular development.

Idelalisib (Zydelig) is indicated for relapsed CLL in combination with rituximab in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities. It's also indicated in relapsed small lymphocytic lymphoma in patients who have received at least two prior systemic therapies. Duvelisib (Copiktra) is indicated for relapsed or refractory CLL or small lymphocytic lymphoma after at least two prior therapies.

Warnings and precautions for idelalisib include hepatic enzyme elevation, severe gastrointestinal symptoms, pneumonitis, and infection.

"It's very important to monitor these patients carefully, especially for sinopulmonary symptoms," said Dr. Kurtin, who noted that a CT of the chest is required to fully characterize pneumonitis. "If patients start experiencing tightness in the chest and shortness of breath, you need to act quickly with monitoring so that they can be treated for pneumonitis with steroids." ●

Disclosure

Dr. Kurtin has acted as a consultant for Celgene and Incyte.

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