CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

Genomic Risk Stratification in Chronic Lymphocytic Leukemia

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H&O Which patients with chronic lymphocytic leukemia (CLL) require treatment?

AW A substantial proportion of patients with CLL can go for decades with no need for treatment. Although CLL can lead to complications such as an increased risk of infections and a possible risk of second primary malignancies, treatment does not reduce those risks and we still do not have a curative therapy. Therefore, we only want to treat patients who have symptoms related to the CLL.

Two common signs of CLL are anemia and thrombocytopenia, both of which are classic indications for treatment. Sustained increases in the absolute lymphocyte count, such as a doubling every 6 months that persists for a couple of years, is another common indication for treatment. Other indications for treatment are massive adenopathy and B symptoms, both of which are rare with CLL in the United States because patients usually receive treatment before their disease progresses to that point.

H&O How do oncologists determine which patients are most likely to experience disease progression?

AW One of the most valuable prognostic markers in CLL is immunoglobulin heavy chain variable region (*IGHV*) mutation status. The *IGHV* gene encodes the antigen specificity of the B-cell receptor expressed on CLL cells. In the 1990s, we first learned that *IGHV* can be either mutated or unmutated in CLL, which came as a surprise because it suggested 2 subtypes of CLL with different cells of origin. Patients with unmutated *IGHV* are more likely to experience progression of CLL from relatively indolent to active disease within a few years. In some studies, the median time from diagnosis to needing treatment in CLL with unmutated *IGHV* is about 3 years.[1,2] In contrast, patients with CLL and mutated *IGHV* tend to have a more indolent disease course, with a median time from diagnosis to needing treatment of 7 years or longer. Another big advantage of *IGHV* testing in CLL is that it only needs to be done once because the mutation status does not change. Although it is valuable to know the *IGHV* mutation status, some patients with *IGHV*-mutated CLL experience progression as if they have the unmutated type. Specifically, patients who have a mutation in the light chain of the B-cell receptor (IGLV3-21^{R}) are more likely to experience progression despite having mutated *IGHV*.[3] The patients who tend to have the worst prognosis are those with *TP53* aberrations, which encompass both del(17p) and mutated *TP53*. These patients derive minimal benefit from chemotherapy.

Another important test is the use of fluorescence in situ hybridization (FISH) to analyze the patient's genetic composition. FISH is useful because the most common genetic abnormalities in CLL are deletions, which are difficult to detect with classic karyotyping. In a 2000 paper in the *New England Journal of Medicine*, Döhner and colleagues systematically used FISH to break down CLL into 5 genetic subgroups: deletion 17p (del[17p]), del(11q), trisomy 12, normal karyotype, and del(13q).[4] They found that del(17p) was associated with the shortest survival and del(13q), the most common genomic aberration, was associated with the longest survival—even longer than for patients with a normal karyotype. The presence of del(11q) was also associated with shorter overall survival (OS). Research since then has begun to dissect CLL into

ever-smaller subgroups. Next-generation sequencing is now able to identify more than 100 gene mutations that are considered drivers of CLL, although this increasingly nuanced information can be hard to translate into clinical practice.

During the chemotherapy era, which lasted from the 1990s until around 2014 or 2015, patients with del(17p) tended to respond poorly to treatment or experienced early relapse. The reason is that del(17p) inactivates the TP53 pathway, which is required for chemotherapy to be effective. Although patients with del(11q) typically respond well to the more intense chemotherapy regimens, they tend to experience relapse. The best available treatment for patients without *TP53* alteration or del(11q) is chemoimmunotherapy with regimens such as fludarabine, cyclophosphamide, and rituximab (FCR), and bendamustine plus rituximab. Many patients experience lasting remission with these therapies, especially those with *IGHV*-mutated disease, lacking del(17p)/mutated *TP53* or del(11q), and receiving FCR. Only a small subset of patients fall into that category and are young enough to tolerate aggressive chemotherapy, however.

Another essential step in determining prognosis is to use the International Prognostic Index for Chronic Lymphocytic Leukemia (CLL-IPI), which integrates genetic and clinical markers.[5] This index factors in del(17p)/*TP53* mutation status, *IGHV* mutation status, serum β_2-microglobulin concentration, Binet or Rai clinical stage, and age.

H&O What are some ongoing studies that are looking at the use of genomic biomarkers in risk stratification?

AW At the biology level, the effort of further dissecting CLL into distinct prognostic and biologic subgroups has continued. An international study by Knisbacher and colleagues identified 202 candidate genetic drivers of CLL, 109 of them new, by integrating genomic, transcriptomic, and epigenomic data from 1148 patients.[6] Based on these data, the team was able to differentiate among 8 subtypes of CLL that had distinct prognoses. This is a fascinating illustration of how CLL is not just a single entity but a rather heterogeneous disease.

The real breakthrough in the treatment of patients with CLL has been the development of targeted therapy. The use of phosphoinositide 3-kinase inhibitors has fallen by the wayside because of their side effect profile, but Bruton tyrosine kinase (BTK) inhibitors, such as ibrutinib (Imbruvica, Pharmacyclics/Janssen), acalabrutinib (Calquence, AstraZeneca), and zanubrutinib (Brukinsa, BeiGene), are effective and well tolerated. The development of BTK inhibitors means that we have a strategy for patients with CLL that does not involve the use of chemotherapy. In the results of a phase 2 trial published in the *New England Journal of Medicine*, we reported a median time until disease progression of 53 months with first-line ibrutinib among 34 patients who had CLL with *TP53* alterations.[7] The estimated progression-free survival (PFS) and OS rates at 6 years were 61% and 79%, respectively. Although this study did not have a comparison group, these results are better than those seen with chemotherapy in other trials. Venetoclax targets BCL2 and effectively restores apoptosis, inducing deep remissions. Time-limited therapy of venetoclax, given for 1 year in combination with obinutuzumab (Gazyva, Genentech) in first-line therapy and for 2 years in combination with rituximab for relapsed or refractory CLL, achieves long-term PFS.[8,9] Although patients with *TP53* alterations achieve good responses with venetoclax-based regimens, the PFS is inferior.[8] Thus, an argument can be made that these patients might be better served by continuous therapy with a BTK inhibitor.

Now that we have 3 BTK inhibitors approved as first-line treatments in del(17p)-type CLL, some studies have started to exclude patients with del(17p) from enrollment in randomized trials containing a chemotherapy arm. This is a good use of the prognostic information we have gained on BTK inhibitors. Other trials allow patients randomized to chemotherapy to cross over to the targeted therapy arm if they experience relapse.

> Among patients who are being treated with continuous BTK inhibitor therapy, relapse is more common in those with del(17p)/mutated *TP53*.

The prognostic value of a given marker depends, in part, on whether the treatment is time-limited or continuous. For example, *IGHV* mutation status has lost some of its prognostic relevance in continuous therapy with BTK inhibitors. In contrast, the duration of response is typically shorter for patients with *IGHV*-unmutated CLL after time-limited therapy. In our study, we are also starting to see differences between *IGHV*-mutated and *IGHV*-unmutated patients on continuous treatment with

ibrutinib, but this took more than 5 years to become apparent.

It remains unclear whether other mutations affect the outcomes with BTK inhibitors, even in the case of *NOTCH1* mutations, which are relatively common. Some studies have reported that *NOTCH1* mutations are a negative prognostic marker for treatment with BTK inhibitors, but other studies have not shown that.

There is also a predictor of response to BTK inhibitors that is not genetic, which is the expression of the integrin CD49d on the cell surface of CLL cells. CD49d plays a role in the migration of lymphoid cells between blood and lymphoid tissues, and it may be a marker of an ability to attach or interact more with the microenvironment. This insight was initially developed by a group in Italy led by Dr Valter Gattei,[10] and we confirmed this in our studies using either ibrutinib or acalabrutinib.[11] Patients with the CD49d-expressing type of CLL were more likely to develop mutations that are associated with resistance to BTK inhibitors.

Moving back to genetic markers, we see that among patients who are being treated with continuous BTK inhibitor therapy, relapse is more common in those with del(17p)/mutated *TP53*. When relapse occurs, most patients show mutations in BTK and/or *PLCG2*. Interestingly, the specific mutations in BTK vary depending on the specific BTK inhibitor used. An interesting question is whether the type of BTK mutation will have importance for the sequencing of therapies.

H&O What is the most practical approach in the clinic?

AW The most practical approach in the clinic is to establish *IGHV* mutation status and del(17p)/*TP53* mutation status to determine which patients need a BTK inhibitor. Beyond that, we still have a lot to learn about how disease stratification affects the treatment approach.

Disclosures

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