Chronic Lymphocytic Leukemia (CLL) is the most common leukemia in adults in the United States, with more than 16,000 people expected to be diagnosed with CLL in 2012. Most patients with CLL do not require treatment at diagnosis. Various genetic/molecular markers to help with prognostication have been established and validated and are routinely used in clinical practice.[1] These include β2-microglobulin, cytogenetics, immunoglobulin variable heavy chain (IGVH) mutational status, Zeta chain–associated protein 70 (ZAP-70) expression, and CD38 expression. The presence of deletion 17p, assessed either by conventional cytogenetics or, more commonly, by interphase fluorescent in situ hybridization (FISH), is associated with the worst clinical outcomes in patients with CLL.[2] In the current issue of ONCOLOGY, Drs. Stephens and Byrd provide a comprehensive overview of the issues pertaining to the management of patients with CLL associated with deletion 17p. Patients with deletion 17p or TP53 gene mutation have poor outcomes with conventional chemoimmunotherapy regimens such as FCR (fludarabine-cyclophosphamide-rituximab [Rituxan]), in part due to lack of wild-type p53 function, an important pathway for mediating the cytotoxicity of purine analogs.[3,4] In the randomized front-line FC (fludarabine-cyclophosphamide) vs FCR German trial, only 1 of the 22 patients with deletion 17p (5%) in the FCR arm achieved complete remission (CR), and the median progression-free survival (PFS) in that arm was only 11.3 months.[3] Similarly, in the German front-line BR (bendamustine [Treanda]-rituximab) trial, none of the 8 patients with deletion 17p achieved CR, and the median PFS was only 7.9 months.[5] These results underscore the need for new management strategies for this group of patients. One strategy would be to consider “early treatment” for patients with deletion 17p, with the goal being to delay disease progression. This strategy is currently being explored in several prospective clinical trials employing treatment regimens such as FCR, lenalidomide (Revlimid), alemtuzumab (Campath), ofatumumab (Arzerra), and others. As mentioned previously, treatment with chemoimmunotherapy for patients with CLL and deletion 17p is suboptimal. In an effort to improve outcomes, many drugs, either as single agents or in combination, have been explored. These include alemtuzumab, alemtuzumab/high-dose corticosteroids, rituximab/high-dose corticosteroids, ofatumumab, lenalidomide and more recently, B-cell receptor (BCR) inhibitors. Results with single-agent alemtuzumab, a humanized monoclonal antibody against CD52, have been similar to results seen with the FCR regimen. Hillmen et al conducted a randomized study of alemtuzumab and chlorambucil and reported a median PFS of 10.7 months in the alemtuzumab arm for patients with deletion 17p (n = 11).[6] These results are similar to those of the randomized German FCR vs FC trial, in which the median PFS for patients with deletion 17p (n = 22) in the FCR arm was 11.3 months.[3] Recently reported results of the CLL206 trial from the United Kingdom showed that use of alemtuzumab with high-dose pulse methylprednisolone (HDMP) was associated with a high CR rate of 65% for previously untreated patients (n = 17) but with a median PFS of only 18.3 months.[7] In contrast to single-agent alemtuzumab, which has limited activity in patients with significant adenopathy, the combination of alemtuzumab and HDMP in the CLL206 trial was equally as effective in patients with significant lymphadenopathy as in those without this finding. BCR inhibitors are showing promising early results in patients with CLL. In a phase IB/II study of the
Bruton tyrosine kinase (BTK) inhibitor ibrutinib, a 65% response rate was seen in the 20 patients with deletion 17p in the relapsed/refractory cohort.[8] This is an impressive response rate for this group of patients, who would otherwise have a dismal prognosis. The estimated 18-month PFS was 87.7% for the entire population (420-mg dose cohort), and this finding was the same across all cytogenetic risk groups.[9] In the older untreated patient cohort of this study, 2 of the 31 patients had deletion 17p, and both of them achieved a response.[9] Brown et al reported on the combination of ibrutinib with bendamustine/rituximab in patients with relapsed/refractory CLL.[10] Of the 30 patients in this study, 7 had deletion 17p, and 5 of these 7 patients (71%) responded, including 1 patient who achieved CR. Thus, it is likely that BCR inhibitors will soon become an integral part of CLL treatment, including for patients with high-risk CLL, such as those with deletion 17p.

Allogeneic stem-cell transplantation (alloSCT) remains the recommended strategy for patients with deletion 17p who achieve a CR. Because most patients with CLL are older than 60 years at the time of diagnosis, reduced-intensity conditioning regimens are typically employed. The preferred approach, until recently, was that all patients with CLL and deletion 17p should have human leukocyte antigen (HLA) typing performed and donor search initiated at the time of therapy initiation, in anticipation of alloSCT in first CR. However, with the demonstrated activity of ibrutinib in patients with deletion 17p, this strategy is being called into question. It is also known that not all patients with CLL and deletion 17p have poor clinical outcomes. There are instances of patients with deletion 17p surviving for more than 10 years without any treatment.[11] Factors associated with longer time to first treatment in those with deletion 17p include mutated IGVH,[11] Rai stage 0 disease,[11] β2-microglobulin < 2 times the upper limit of normal, and ZAP-70 negativity.[12] Patients with CLL and deletion 17p who meet these clinical criteria may not benefit from aggressive treatment strategies.

We congratulate Dr. Byrd and Dr. Stephens for the excellent review of clinical data pertaining to patients with deletion 17p, and we hope that newer therapies, such as BCR inhibitors, will significantly improve outcomes for these patients.

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