Optimal First-Line Therapy for Previously Untreated Chronic Lymphocytic Leukemia: The Case for Kinase Inhibitors


Given the favorable results seen thus far, there is no doubt that the treatment of patients with chronic lymphocytic leukemia is entering an exciting new era with the advent of these novel, relatively nontoxic and nonmyelosuppressive, oral agents.

The traditional approach to therapy for previously untreated patients with chronic lymphocytic leukemia (CLL) has been chemoimmunotherapy programs (whether FCR [fludarabine, cyclophosphamide, rituximab], FR [fludarabine, rituximab], BR [bendamustine, rituximab], PCR [pentostatin, cyclophosphamide, rituximab], other. These combination treatments have led to increased rates of clinical remission, with the frequency of complete responses (CRs) ranging from 23% to 79%, depending upon the study reported.[1-7] While they are extremely active regimens, the available chemoimmunotherapy treatments have been limited by enhanced myelosuppression and immunosuppression, often leading to dose reductions or early discontinuation of therapy and thereby precluding their full clinical benefit.

Moreover, the median age at diagnosis of chronic lymphocytic leukemia is 72 years, and this issue is more notable in the older patient population. For example, as reported in the German CLL 8 trial, in which relatively young and fit previously untreated patients with chronic lymphocytic leukemia were enrolled, there was still a treatment discontinuation rate of 26%. [1] In the chemoimmunotherapy arm, the planned dose was reduced by more than 10% in 189 of 404 patients (47%); 33% experienced > 10% dose reductions during the first to third courses of treatment, and 34% required dose reductions by > 10% during the fourth to sixth courses of therapy. These dose reductions were mostly due to treatment-related hematologic toxicity, in particular neutropenia and leukocytopenia, which occurred in 117 of 189 patients (62%) in the chemoimmunotherapy group). Investigators at The University of Texas MD Anderson Cancer Center also noted early discontinuation in 26% of patients, as well as long-term cytopenias, particularly in patients > 65 years of age treated with FCR.[2,8] In addition, given that patients with chronic lymphocytic leukemia may receive multiple therapies during their lifetime, repeated use of these more aggressive combination regimens is often limited by mounting treatment toxicities, poorer patient immune function, and decreased therapeutic efficacy over time.

Fortunately, over the past 5 years, there has been an explosive development of several small-molecule inhibitors that interrupt the B-cell receptor signaling pathway that is critical in the development, expansion, and survival of both normal and malignant B cells. These oral agents have shown remarkable activity in previously untreated or relapsed, refractory disease, as well as in patients who harbor cytogenetic abnormalities associated with poor prognosis.[9-18] They have the added benefit of being more selective, as they target several of these key proteins (eg, Bruton’s tyrosine kinase [BTK], phosphatidylinositol 3 kinase [PI3K], and spleen tyrosine kinase [Syk]), with less toxicity than traditional chemoimmunotherapy programs. In addition, patients with poor-risk cytogenetics (eg, 17p deletion) or unmutated immunoglobulin heavy chain variable gene (IGHV) often have inferior responses to most traditional treatments, with shorter response durations and decreased overall survival (OS). Some of these oral agents have already demonstrated a superior progression-free survival (PFS) and an OS advantage in high-risk relapsed/refractory patients.

The BTK inhibitor ibrutinib is the most well studied of these agents. Byrd et al recently reported on the 3-year follow-up of patients treated with ibrutinib in a study of previously untreated patients ≥ 65 years of age with chronic lymphocytic leukemia treated in the original phase Ib/II study.[13] The median duration of therapy in this group is 30 months (range, 0.3–44 months). Notably, with 3 years of follow-up, 81% of these patients still remain on ibrutinib therapy. The overall response rate was 84%, with 23% of patients achieving a CR with single-agent ibrutinib. Also importantly, it was noted that with continued ibrutinib therapy, both the quality and frequency of responses increased over time (with a median time to CR of 21 months). The median PFS has not yet been reached, and the
estimated 30-month OS is 96%. The most common adverse events (AEs) observed over the 3-year period were hypertension (23%); diarrhea (16%); infections, including pneumonia (13%); and atrial fibrillation (6%). The rate of cytopenias was less than 5%. Moreover, it was noted that the frequency of cytopenias, pneumonia, diarrhea, and other less commonly occurring AEs declines over time. Only 10% discontinued therapy due to AEs, and one patient had disease progression. In addition, ibrutinib has been approved for patients with 17p deletion based on the results of the phase III RESONATE study, in which patients who were randomized to ibrutinib (vs ofatumumab) experienced a significant reduction in risk of disease progression or death.[14] Of the 127 participants who had chronic lymphocytic leukemia with 17p deletion, those treated with ibrutinib experienced a 75% reduction in risk of disease progression or death.

Idelalisib, a PI3K inhibitor, is also approved in combination with rituximab for use in previously treated patients with chronic lymphocytic leukemia. In a study reported by Furman et al, 220 patients with decreased renal function, myelosuppression caused by previous therapy, or major coexisting illnesses were randomized to receive rituximab and either idelalisib (at 150 mg) or placebo twice daily.[17] The primary endpoint was PFS, and at the first prespecified interim analysis the study was stopped early by the data and safety monitoring board due to overwhelming efficacy favoring the idelalisib/rituximab combination. The median PFS was 5.5 months in the placebo group and was not reached in the idelalisib group. Patients receiving idelalisib vs those receiving placebo had improved rates of overall response (81% vs 13%) and OS at 12 months (92% vs 80%). Serious AEs occurred in 40% of the patients receiving idelalisib and rituximab and in 35% of those receiving placebo and rituximab. Similarly, O’Brien et al, in a phase II study of idelalisib with rituximab in 64 previously untreated patients with chronic lymphocytic leukemia, showed a 97% overall response frequency, with 19% complete remissions and 93% PFS at 24 months.[18] In this study, the nine patients with 17p deletion all experienced a response, including three with complete remissions, and none have experienced disease progression to date. The primary toxicities with idelalisib have included increased levels of hepatic transaminases, usually readily manageable by interrupting the drug, and diarrhea including colitis in a subset of patients.

Currently, there are several phase III studies, either closed to accrual or ongoing, that will answer the question of whether these novel kinase inhibitors administered in the frontline setting will prove to have a favorable impact on PFS or OS with decreased toxicity, compared with more traditional chemoimmunotherapy regimens like FCR or BR. In addition, studies evaluating the combination of these novel agents with more traditional therapies will soon be reported. Given the favorable results seen thus far, there is no doubt that the treatment of patients with chronic lymphocytic leukemia is entering an exciting new era with the advent of these novel, relatively nontoxic and nonmyelosuppressive, oral agents.

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References:


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