CLL IN FOCUS

News in the Treatment of Chronic Lymphocytic Leukemia

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CLL Linked to Elevated Risk for Second Cancers Even With BTK Inhibition

Patients with chronic lymphocytic leukemia (CLL) are at increased risk for second cancers even when they are treated with Bruton tyrosine kinase (BTK) inhibitors, according to a new study. This finding makes the detection of a secondary cancer especially important in this population.

For the study, which was published online July 23 in *Leukemia*, Dr David A. Bond and colleagues reviewed the electronic medical records of all adults with CLL who had received ibrutinib (Imbruvica, Pharmacyclics/Janssen) or acalabrutinib (Calquence, AstraZeneca) at The Ohio State University Comprehensive Cancer Center between December 2009 and December 2017. The researchers identified 691 patients with complete medical records. The patients had received a median of 2 prior lines of therapy, including a purine nucleoside analogue in 55% and alkylating chemotherapy in 60%. The BTK inhibitor was ibrutinib in 79% of patients and acalabrutinib in 21% of patients. Median follow-up was 44 months.

Nonmelanoma skin cancer was diagnosed in 20% of patients and Richter syndrome in 8% of patients after they had started a BTK inhibitor. When these 2 diagnoses were excluded, an invasive second primary malignancy was diagnosed in 9% of patients. The rate of secondary primary malignancies was more than double the expected rate, with a standardized incidence ratio of 2.2. Multivariable analysis revealed an increased risk for a secondary primary malignancy associated with smoking (hazard ratio [HR], 2.8; 95% CI, 1.6-4.8) and a decreased risk for a secondary primary malignancy associated with a higher baseline CD8 cell count (HR, 0.9 [95% CI, 0.8-0.9] with a 2-fold increase in the cell count).

The researchers wrote that quantitative lymphocyte count changes represent a "potential biomarker" for a risk for secondary malignancies in patients with CLL.

CLL Linked to Increased Risk for Symptomatic COVID-19

People with CLL may be at elevated risk for acquiring coronavirus disease 2019 (COVID-19) and dying of it, according to a European study. The study also suggested that certain CLL treatments may improve COVID-19 outcomes in these patients.

The study, which was undertaken by the European Research Initiative on CLL (ERIC) and CLL Campus, was published online July 9 in *Leukemia* with Dr Lydia Scarfò as the first author. The researchers identified 190 patients with CLL and a confirmed case of COVID-19 diagnosed between March 28 and May 22 of this year. Most of the patients (97%) were European, and 90% of the European patients were from Italy or Spain. Most of the patients (79%) presented with severe COVID-19, defined as requiring oxygen or admission to an intensive care unit.

As expected, patients aged 65 years and older were more likely than younger patients to have severe COVID-19 (odds ratio, 3.72; 95% CI, 1.79-7.71). The COVID-19 mortality rate was 36% for those with severe disease vs 3% for those with mild disease, but age and comorbidities did not affect mortality.

The researchers also found that patients with severe COVID-19 were less likely to be receiving current treatment or to have had recent treatment for CLL (40%) than were those with mild COVID-19 (77%). Further, the hospitalization rate for severe COVID-19 was lower among patients on ibrutinib than among those on other regimens or not on treatment.

The authors concluded that although patients with CLL may be at elevated risk for symptomatic COVID-19 and COVID-19 mortality, some treatments (in particular BTK inhibitors) may have a "potential protective role" in the clinical course of disease, decreasing morbidity and mortality in these patients.

Addition of Ibrutinib to Chemoimmunotherapy Continues to Benefit Overall Survival

The addition of ibrutinib to chemoimmunotherapy with bendamustine (Treanda/Bendeka; Teva) plus rituximab continues to benefit overall survival (OS) in patients with relapsed or refractory CLL or small lymphocytic leukemia (SLL), according to 5-year results from the HELIOS study. This finding is consistent with the 3-year results from the trial.

For the phase 3, double-blinded study, which was published online August 6 in *Leukemia & Lymphoma*, Dr Graeme Fraser and colleagues randomly assigned 578 adults who had relapsed or refractory CLL/SLL without 17p deletion either to ibrutinib at 420 mg/d or to

placebo, plus up to 6 cycles of bendamustine/rituximab. These regimens were followed by ibrutinib or placebo alone, respectively. Patients had received a median of 2 prior lines of therapy.

Nearly two-thirds of patients (63.3%) crossed over from the placebo arm to the ibrutinib arm. Nonetheless, median progression-free survival (PFS) after a median follow-up of 63.7 months was significantly longer in the ibrutinib group than in the placebo group, at 65.1 vs 14.3 months (HR, 0.23; 95% CI, 0.18-0.29; *P*<.0001), respectively. In addition, OS was significantly longer in the ibrutinib group than in the placebo group (HR, 0.61; 95% CI, 0.46-0.82; *P*=.001). The overall response rate also was significantly higher in the ibrutinib arm than in the placebo arm, at 87.2% vs 66.1% (*P*<.0001), respectively.

The rate of complete response or complete response with incomplete hematologic recovery was 41%, which was significantly higher than the 21% figure reported at the interim analysis. This finding reflected "the ongoing benefit of continuous treatment with ibrutinib," wrote the authors.

The authors added that the long-term safety findings for the ibrutinib plus bendamustine/rituximab arm were consistent with the known safety profiles of these agents.

First-line Ibrutinib Provides Long-term Benefit in CLL With TP53 Alterations

First-line ibrutinib provides long-term benefit to people with CLL and *TP53* alterations even when the treatment does not lead to undetectable measurable residual disease (MRD), according to the results of a phase 2 study.

For the study, which appeared as a letter in the July 30 issue of the *New England Journal of Medicine*, Dr Inhye Ahn and colleagues administered ibrutinib as first-line therapy to 34 patients with CLL and *TP53* alterations. The median age of the patients was 63 years.

Of the treated patients, 30% had a complete response as best response, and 1 patient had undetectable MRD. At a median follow-up of 6.5 years, a total of 17 patients remained in the study, including 6 patients who had a complete response.

The estimated 6-year PFS rate was 61%, and the estimated 6-year OS rate was 79%. The median time until disease progression was 53 months. Of the 12 patients with disease progression while on ibrutinib, 4 had histologic transformation and 8 had progression of CLL. The immunoglobulin heavy chain variable region gene (*IGHV*) was unmutated in 11 of the 12 patients with disease progression. PFS was longer in the patient with mutated *IGHV* than in those with unmutated *IGHV*.

Side effects were consistent with the results of previous studies, and reductions in dose were uncommon, occurring in 6% of the patients. The most common reason for discontinuation of ibrutinib was disease progression.

The investigators noted that patients derive long-term benefit with ibrutinib "despite the lack of achievement of undetectable levels of MRD." They added that this finding suggests that "deep remission is not a prerequisite for a durable response."

Single-Agent Ibrutinib Produces Sustained Responses in CLL/SLL

Single-agent ibrutinib produces sustained responses and has long-term tolerability in patients with CLL or SLL, whether used as first-line treatment or in relapsed/refractory disease. This finding was based on follow-up lasting up to 8 years in the phase 1b/2 PCYC-1102 study and a related extension study, PCYC-1103. The final analysis of both trials was published by Dr John Byrd and colleagues August 1 in *Clinical Cancer Research*.

In the open-label, nonrandomized PCYC-1102 study, adults with CLL or SLL received ibrutinib at 420 or 840 mg/d in 28-day cycles until disease progression or unacceptable toxicity. After the primary analysis, patients who completed at least 6 cycles of treatment without disease progression were eligible for PCYC-1103, an open-label extension study. A total of 132 patients were followed: 31 in a first-line treatment group for a median of 87 months and 101 in a relapsed/refractory group for 82 months.

The overall rate of response to ibrutinib was 89%, with similar rates for those in the first-line setting (87%) and the relapsed/refractory setting (895). The estimated 7-year PFS rate was 83% in the first-line group and 34% in the relapsed/refractory group. Progression of CLL occurred in a total of 41 patients, Richter transformation in 11 of them.

Median PFS was not reached in the first-line setting. Among those with relapsed/refractory CLL/SLL, median PFS was 52 months overall, 26 months in those with del(17p), 51 months in those with del(11q), not reached in those with trisomy 12 or del(13q), and 88 months in those without these cytogenetic abnormalities. The estimated OS rate was 84% in the first-line setting and 55% in the relapsed/refractory setting. Grade 3 or higher adverse events included hypertension (28%), pneumonia (24%), and neutropenia (18%).

The authors concluded that "the sustained disease control and acceptable tolerability observed with prolonged single-agent ibrutinib treatment provides strong evidence for use in patients with CLL/SLL, even those with unfavorable disease characteristics."