Adding Ibrutinib to Standard Therapy Reduces Disease Progression by 80% in Previously Treated Patients with CLL

By Phoebe Starr

Chicago, IL—The combination of ibrutinib (Imbruvica) plus standard therapy with bendamustine (Treanda) and rituximab (Rituxan) significantly reduced the risk for disease progression or death by 80% compared with bendamustine plus rituximab alone in previously treated patients with chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL), according to lead investigator Asher A. Chanan-Khan, MD, Chair, Division of Hematology/Oncology, Mayo Clinic, Jacksonville, FL.

These results come from HELIOS, one of the largest phase 3 trials in this setting, and were presented at ASCO 2015.

"There are countless patients with CLL for whom this drug is a blessing. Ibrutinib reduced the risk of progression or death by 80%. This is an impactful therapy that changes the course of disease early on," said Dr Chanan-Khan.

Photo by © ASCO/Scott Morgan 2015

> "There are countless patients with CLL for whom this drug is a blessing. Ibrutinib reduced the risk of progression or death by 80%."
>
> —Asher A. Chanan-Khan, MD

Comparing Novel Targeted Drug and Chemoimmunotherapy

HELIOS is the first placebo-controlled study of ibrutinib in CLL/SLL and the first large phase 3 trial to evaluate a novel targeted drug with chemoimmunotherapy.

The randomized, double-blind, international HELIOS trial included 578 patients with previously treated CLL/SLL requiring therapy to receive ibrutinib plus standard bendamustine and rituximab, followed by ibrutinib maintenance or placebo plus bendamustine and rituximab, followed by placebo maintenance.

The treatment was given for a maximum of 6 cycles, and maintenance therapy was continued until progression or unacceptable toxicity. Crossover to ibrutinib maintenance was allowed for patients with progressive disease in the placebo maintenance arm. Any patients with deletions in 17p were excluded.

At baseline, 26% of the patients were purine analog–refractory. Approximately 49% of the patients received 1 previous line of therapy, approximately 25% received 2 previous lines, and approximately 26% received ≥3 previous lines of therapy.

The primary end point was progression-free survival as assessed by an Independent Review Committee. At 17 months of follow-up, the median progression-free survival had not yet been reached in the group receiving ibrutinib, but it was 13.3 months with standard bendamustine and rituximab (P <.001). Ibrutinib significantly reduced the risk for progression or death by 80% compared with placebo plus bendamustine and rituximab.

Ibrutinib was favored in all of the subgroups that were analyzed, including age, sex, diagnosis, Rai stage at screening, previous lines of therapy, bulky disease, baseline Eastern Cooperative Oncology Group status, and the presence or absence of deletions in 11q and immunoglobulin VH.

At a median follow-up of 17.2 months, the overall survival had not been reached in either arm. Ibrutinib reduced the risk for death by 37% (P = .05598). Dr Chanan-Khan noted that the survival results are confounded by crossover to single-agent ibrutinib for maintenance by 90 patients in the placebo arm (31%).

The overall response rate was significantly higher in the ibrutinib plus bendamustine and rituximab arm (82.7%) versus the placebo plus bendamustine and rituximab arm (67.8%).

No unexpected side effects were reported. The safety profiles were consistent for each of the drugs. The most frequent side effects were low blood cell counts, nausea, and diarrhea.

"These results represent a changing point in the treatment of CLL. The standard of care should now be ibrutinib plus bendamustine and rituximab for previously treated patients," Dr Chanan-Khan stated. ■

Adherence to Ibrutinib Therapy Improves Outcomes in Patients with CLL

By Laura Morgan

A subanalysis of the phase 3 clinical trial RESONATE showed that adherence to the recommended dose of ibrutinib in patients with chronic lymphocytic leukemia (CLL) who had received previous therapy improved extended progression-free survival (PFS) compared with patients who did not adhere to the treatment regimen, suggested Paul Barr, MD, Assistant Professor of Medicine and Director of the Clinical Trials Office, Wilmot Cancer Institute, Rochester, NY, who presented the results at ASCO 2015.

The randomized, multicenter, international, head-to-head RESONATE trial included 373 patients with CLL and 18 patients with small lymphocytic leukemia. Patients were randomized to once-daily, 420-mg orally administered ibrutinib, a first-in-class inhibitor of Bruton's tyrosine kinase inhibitor, or to intravenous ofatumumab, a CD20 antigen inhibitor. The most common nonhematologic adverse events observed in patients who received ibrutinib included diarrhea, fatigue, pyrexia, and nausea.

The goal of this subanalysis of RESONATE was to investigate the impact of adhering to the recommended dose of ibrutinib in patients with CLL. A total of 195 patients with previously treated CLL received 420 mg of ibrutinib for 8.3 months. At the end of the treatment period, the mean dose intensity—defined as the proportion of actually used doses versus planned doses of ibrutinib 420 mg—was 95%. Overall, the majority of dose interruptions reinstated the 420 dose after the dose reduction: 3.6% of the patients had 1 dose reduction and 0.5% had 2 dose reductions because of adverse events.

The PFS duration was longer among patients who used the recommended 420-mg dose of ibrutinib (median not yet reached at the time of the analysis) compared with 11 months for the patients who took lower doses. This had no relation to high-risk factors in this patient population (such as deletion 17p or *p53* mutation).

> "These data show that when patients take Imbruvica daily, at the recommended dose, it can improve their chance of achieving a sustained treatment response and delay disease progression."
>
> —Paul Barr, MD

Furthermore, patients who missed the recommended ibrutinib dose for ≥8 consecutive days had significantly more adverse events compared with patients who adhered to the recommended 420-mg dose (33% vs 13%, respectively).

"These data show that when patients take Imbruvica daily, at the recommended dose, it can improve their chance of achieving a sustained treatment response and delay disease progression," Dr Barr said. "As clinicians, it is important that we ensure that patients take this once-daily, oral medication as recommended in order to achieve the best possible outcome in treating their cancer." ■