Venetoclax–Rituximab Combination Therapy Improves Progression-Free Survival Rate in Chronic Lymphocytic Leukemia

Venetoclax–rituximab combination therapy improves progression-free survival rate and overall survival in patients with relapsing or refractory chronic lymphocytic leukemia.

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May 2, 2018 – In patients with relapsing or refractory chronic lymphocytic leukemia (CLL), treatment with venetoclax-rituximab combination significantly improved the rates of progression-free survival and overall survival, the phase III MURANO trial showed.

John F. Seymour, MBBS, PhD, with the Peter MacCallum Cancer Centre in Australia, reported the findings of an international, open-label study in the March 22, 2018 issue of *The New England Journal of Medicine.*

Venetoclax is an inhibitor of the antiapoptotic protein BCL-2. As a monotherapy, venetoclax induces CLL cell apoptosis and improves the quality of response in patients with heavily pretreated CLL. In this randomized study, the investigators assessed the potential of a combination therapy using venetoclax and an anti-CD20 antibody, rituximab, to improve progression-free and overall survival in patients with relapsing or refractory CLL.

A total of 389 patients (≥18 years) were randomly assigned in a 1:1 ratio to receive either venetoclax-rituximab (n=194) or the standard chemoimmunotherapy (control; n=195). Presence or absence of chromosome 17p deletion, responsiveness to previous treatment, and geography were used to stratify the randomized groups.

Patients received gradually increasing oral doses of venetoclax (20-400 mg/day) for the first 5 weeks. After the dose ramp-up, 400 mg/day venetoclax was continued for up to 2 years along with intravenous rituximab (first dose: 375 mg/m^2; 500 mg/m^2) for the first 6 months in 28-day treatment cycles. In the control group, patients received 70 mg/day of bendamustine intravenously along with described dose regimen of rituximab for the first 6 months.

Investigator-assessed progression-free survival was the primary endpoint of the study. The secondary endpoints included: overall survival, the clearance rate of minimal residual disease, event-free survival, response duration, independent review committee (IRC)-assessed progression-free survival, time to the next treatment for CLL, and investigator and IRC-assessed progression-free survival and response rate of patients with chromosome 17p deletion.

The venetoclax-rituximab group fared significantly better than the control group in every endpoint tested and across all the stratified groups. The results were verified and confirmed by an IRC.

The 2-year investigator-assessed progression-free survival rate was 84.9% in the venetoclax-rituximab group compared with 36.3% in the control group (hazard ratio [HR] for progression or death, 0.17; 95% CI, 0.11-0.25; P<0.001). At the median follow-up of 23.8 months, a significantly smaller number of disease progression events were reported in the venetoclax-rituximab group (32/195) compared with the control group (114/195).

The progression-free survival rate was significantly higher in the venetoclax-rituximab group compared with the control group amongst patients with chromosome 17p deletion (81% vs 27.8%; HR, 0.13; 95% CI, 0.05-0.29) and without the deletion (85.9% vs 41%; HR, 0.19; 95% CI, 0.12-0.32).

Neutropenia is a known adverse event associated with venetoclax. In the test group, higher incidences of grade 3 or 4 neutropenia (60.8%) were reported compared with the control group (44.1%). Grade 3 or 4 tumor-cell lysis syndrome was also reported in the venetoclax-rituximab (3.1%) and in the control (1.1%) group. The rates of grade 3 or 4 infections or infestations were higher in the control group than the venetoclax-rituximab group.

"The substantial rate of clearance of minimal residual disease in the venetoclax–rituximab group may indicate improved disease control over a longer term even when therapy is discontinued," concluded Dr John F. Seymour and colleagues.

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Seymour JF, Kipps TJ, Eichhorst B, et. al., Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *N Engl J Med*. 2018; 378:1107-1120.