T.S. Lin

Division of Hematology and Oncology,
The Ohio State University,
Columbus, OH USA

Lumiliximab in chronic lymphocytic leukemia

Lumiliximab is an anti-CD23 monoclonal antibody that is being investigated for the treatment of relapsed B-cell CLL. CD23 is a glycoprotein expressed on the majority of CLL cells. Preclinical data shows synergy of lumiliximab with both fludarabine and rituximab.[1] Lumiliximab monotherapy given weekly or thrice weekly for 4 weeks to patients with relapsed CLL was well tolerated, achieved sustainable CD23 receptor occupancy and showed clinical activity.[2] A decrease in ALC was seen in 91% of patients; decrease in lymph node bulk was noted in 52%. A Phase I/II, multiceneter study was conducted to evaluate the safety and efficacy of lumiliximab in combination with fludarabine, cyclophosphamide, and rituximab (L+FCR) for patients with relapsed CLL. Correlative studies included CD23 receptor occupancy on CLL cells, possible effects of elevated serum CD23, relationship of response to baseline presence of CD38 and ZAP 70 (negative prognostic markers), CD55 and CD59 (potential resistance markers to rituximab).[3-5] Thirty-one pts with relapsed CLL received either 350 mg/m^2 (n=3) or 500 mg/m^2 (n=28) of L + FCR (Fludarabine 25 mg/m^2/day x 3, cyclophosphamide 250 mg/m^2/day x 3, rituximab 375 mg/m^2 x 1 on cycle 1 and 500 mg/m^2 x 1 on subsequent cycles) for up to six 28-day cycles. All pts completed treatment and follow-up is ongoing. Median age at study entry was 58 yrs, 71 % had Rai stage I/II disease, and the median number of prior regimens was 2 (1-10). Using NCI-WG criteria, overall response rate was 65% complete response (CR) 52% and partial response (PR) 13%.

Based on median follow-up of 16.8 mos (1.5-37.6) and KM estimated analyses, median progression-free survival (PFS) for all pts was 19.3 mos. Median PFS for all responders and CR pts were 23.4 mos and 30.4 mos, respectively. Twenty-three pts (74%) reported a Grade 3 or 4 event. Compared with previously published FCR data in relapsed CLL[6], L+FCR has a similar safety profile with no additional toxicities. Of note, the CR rate in the historical population (FCR alone) was 25% versus 52% with L+FCR regimen. L+FCR sustained CD23 receptor occupancy which was not affected by elevated levels of serum CD23.

Clinical activity was seen in patients expressing ZAP70 and CD38 and was independent of pretreatment expression levels of CD55 and CD59.

These results suggest that L+ FCR is an effective regimen for pts with relapsed B-CLL. L+FCR produced an impressive CR rate,

an encouraging PFS, and a similar safety profile to that of FCR. A large, randomized, global study of L+FCR vs FCR (LUCID) is ongoing to further evaluate the safety and efficacy of this regimen.

References

1. Pathan NI, Chu P, Hariharan K, Cheney C, Molina A, Byrd J. Mediation of apoptosis by and antitumor activity of lumiliximab in chronic lymphocytic leukemia cells and CD23+ lymphoma cell lines. Blood 2008;111:1594-602.
2. Byrd JC, O'Brien S, Flinn IW, Kipps TJ, Weiss M, Rai K, et al. Phase 1 study of lumiliximab with detailed pharmacokinetic and pharmacodynamic measurements in patients with relapsed or refractory chronic lymphocytic leukemia. Clin Cancer Res 2007;13:4448-55.
3. Byrd JC, Castro J, Flinn IW, Forero-Torres A, Kipps TJ, Heerema NA, et al. Lumiliximab in combination with FCR for the treatment of relapsed chronic lymphocytic leukemia (CLL): Results from a phase I/II multicenter study. J Clin Oncol 2008;26(15S):372s.
4. Pathan N, Estrellado A, Ranuio J, O'Brien S, Kipps TJ, Cesano A, et al. Correlation of clinical activity of lumiliximab in combination with FCR and ZAP 70 expression on B-cell chronic lymphocytic leukemia cells. J Clin Oncol 2008;26(15S):390s.
5. Tangri S, Ranuio J, Estrellado A, Byrd JC, O'Brien S, Kipps TJ, et al. Immunophenotypic characterization of relapsed chronic lymphocytic leukemia patients treated with lumiliximab in combination with FCR. J Clin Oncol 2008;26(15S):388s.
6. Wierda W, O'Brien S, Wen S, Faderl S, Garcia-Manero G, Thomas D, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. J Clin Oncol 2007;23:1-9.