IWWM-10 Session 2: Thursday, October 11, 2018, Varettoni

Is detection of mutated MYD88 associated with progression of IGM MGUS?

Marzia Varettoni, Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Waldenstrom's Macroglobulinemia (WM) may be preceded by a history of IgM monoclonal gammopathy of undetermined significance (IgM MGUS). In a recent study including 210 patients with IgM MGUS with a median follow-up of 29.3 years, Kyle et al. demonstrated that the risk of progression was 2% per year in the first 10 years and 1% per year thereafter. The initial concentration of the serum monoclonal protein and the serum free light-chain ratio were independent risk factors for progression in multivariate analysis. From a biological standpoint, transition from IgM MGUS to WM is probably a multi-step process, where multiple genetic hits are required for progression from a pre-benign condition to a neoplastic disease. The MYD88 (L265P) mutation, which is present in more than 90% of patients with WM, is detectable in about half the patients with IgM MGUS. In a retrospective study on 136 IgM MGUS patients studied with allele-specific polymerase chain reaction (AS-PCR), we demonstrated that the MYD88 (L265P) mutation was an independent risk factor for progression, irrespective of the concentration of the serum monoclonal protein.

We have now studied a larger series of patients with IgM MGUS or IgM-related disorders, diagnosed according to the criteria established during the second International Workshop on WM. The primary objective of this study was to assess whether the MYD88 mutation status and/or the MYD88 allelic burden was a risk factor for progression to WM or to other lymphoproliferative disorders. Patients for whom a bone marrow biopsy was not performed or was not evaluable were excluded from the analysis. The MYD88 mutation status was evaluated with allele specific real-time quantitative polymerase chain reaction (AS-qPCR) on bone marrow samples collected at diagnosis. Cell lines OCI-LY19 (MYD88 wt) and OCI-LY3 (MYD88 mutated, L265P) were used to construct two different standard curves by dilution series of 7 different concentrations ranging from 40 ng/µl to 0.08 ng/µl. Allele burden quantification was defined as the ratio MYD88 L265P mutant/MYD88 mutant and wild-type alleles. The results of this study will be presented during the meeting.