RECENT ADVANCES IN DIAGNOSIS, MOLECULAR PATHOLOGY AND THERAPY OF WALDENSTROM MACROGLOBULINEMIA.

Adriana Colita[1], A.Colita[2], D.Coriu[1]
1 Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Bucharest
2Clinic of Hematology, Coltea Clinical Hospital, Bucharest

Waldenström macroglobulinemia (WM) is a rare lymphoid neoplasm resulting from the accumulation, predominently in the bone marrow (BM), of a clonal population of lymphocytes, lymphoplasmocytic cells and plasma cell wich secrete a monoclonal immunoglobulin M (IgM). According to WHO classification, WM is classified as a lymphoplasmocytic lymphoma (LPL/WM). The origin of the malignant clone is thought to be an arrested B cell that has undergone somatic hypermutation in germinal center without differentiating to plasma cell. The most common cytogenetic abnormality is 6q deletion detected in 50% of cases with WM and is associated with an adverse prognosis. Recently, whole genome sequencing has discover two activating somatic mutations: MYD88 L265P (in chromosome 3p22.2) and WHIM-like CXCR4, associated with significant differences in clinical presentation and survival. MYD88 L265P are found in 90-95% of WM patients and may help to differentiate WM from other lymphoproliferative disorders with overlapping feature (SMZL, LLC, IgM-MM). MYD88 L265P is a molecular biomarker of WM. Risk factors for developing WM: pre-existing IgM-MGUS, familial hystory, immunological factors. The diagnostic criteria for WM: IgM monoclonal gammapathy of any concentration; bone marrow infiltration by small lymphocytes showing plasmocytoid or plasma cell differentiation; intertrabecular pattern of bone marrow infiltration; surface IgM+ CD5± CD10- CD19+ CD20+ CD22+ CD23- CD25+ CD27+ FMC7+ CD103- CD138- immunophenotype. The clinical manifestations include those related to clonal cell infiltration of bone marrow, limph node, liver, spleen. Manifestations related to the IgM monoclonal protein include hyperviscosity, cryoglobulinemia, antibody mediated disorders (neuropathy, hemolitic anemia, Schnitzer syndrome), amyloidosis. Prognosis of WM depends on 5 major factors (IPSS-WM): age, hemoglobin level, platelet count, B2 microglobulin and monoclonal IgM concentration. Treatment decision are based on the presence of symptoms, patients factors (age, performance status), diseases factors (citopenias, significance adenopathy or organomegaly, symptomatic hyperviscosity, neuropathy, amyloidosis, cryoglolinemia, cold aglutinin disease, evidence of disease transformation). Current treatment options include alkylating agent, purine analogues, monoclonal antibody (Rituximab), proteasomal inhibitor. Plasma exchange is a treatment indicated for acute management of hyperviscosity syndrome. Agents under study: everolimus, carfilzomib. High-dose chemotherapy with autologous stem cell rescue in primary refractory or relapsed disease shoud be considered for eligible patients. Novel target therapeutic strategies directed against MYD88 signaling (ibrutinib) and CXCR4 (plerixafor) are in clinical investigations.