

[Abstract 23]

ROLE OF THE FC γ RECEPTORS (FC γ R1IA AND 11IA POLYMORPHISMS IN WALDENSTROM'S MACROGLOBULINEMIA

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Context : Waldenström's macroglobulinemia (WM) is a B-cell lymphoplasmatic disorder of the bone marrow characterized by a monoclonal immunoglobulin M (IgM) in the serum. Autoimmune disorders such as cryoglobulinemia and hemolytic anemia may occur at diagnosis or later in the course of evolution. Polymorphisms corresponding to phenotypic expression of valine (V) or phenylalanine (F) at amino acid 158 of Fc γ R11a receptor (Fc γ R11a (V/F) and of histidine (H) or arginin (A) at amino acid 131 of Fc γ R11a [Fc γ r11a (R /H)] greatly influence the affinity of IgG for the Fc γ receptor, the effectiveness of the clearance of immune complexes in vivo, and consequently the clinical manifestations and course of autoimmune disease (Arthritis Rheum. 2003, 48:1930). Therefore, we assessed the distribution of autoimmune disorders according to these different function-related genetic polymorphisms in WM.

Materials and Methods : Genotype distribution was determined in 23 pts with Ig M MGUS and in 66 patients (pts) with WM (median age : 64 years, range 39 to 98, M/F=2) diagnosed between 1983 and 2004. Cryoglobulinemia was found in 9 pts (type I: 5, type II: 1, undetermined: 3). Hemolytic anemia occurred in 7 pts. Direct antiglobulin test (DAT) detected IgG, and C3d in 10 and 5 pts respectively. At the date of the analysis, 20 asymptomatic pts were untreated. First line therapy included chlormabucil in 34, combination chemotherapy (ct) in 2, purine analog alone in 6, or in combination with other ct in 3, and rituximab in 1 pt. In addition, 10 pts received monoclonal antibody therapy and 14 fludarabine later during their evolution. Fc γ R11a (R /H) and Fc γ R11a (V/F) polymorphism were genotyped using a PCR-RFLP assay.

Results: Of the 66 WM, 26% were homozygous for R, 26% homozygous for H and 48% heterozygous (RH pts), and 14/58 pts were homozygous for F allele (Fc γ R11a FF). The allele frequencies of Fc γ R11a (H) and Fc γ R11a (F) were 0.47 and 0.50 respectively. The genotype distributions in WM pts and IgM pts were not significantly different for Fc γ R11a R/H and Fc γ R11a V/F polymorphisms. Fc γ R11a HH patients more frequently presented with thrombocytopenia (p=0.02), multiple cytopenias (p=0.02). DAT detected more frequently IgG (p=0.01) in HH pts. In addition, HH pts more frequently had hemolytic autoimmune anemia and cryoglobulinemia than RH pts (p=0.03 and p=0.04 respectively). RR pts more frequently had IgG positive DAT than RH pts (p=0.008). Clinical course was evaluated in 46 patients diagnosed before June 2003. RR pts and HH pts had a shorter survival than RH pts (p=0.02 and p=0.04 respectively). By contrast, There was no significant differences in overall survival or clinical presentation between Fc γ R11a F/F pts and remaining pts.

In conclusion, our preliminary results suggested that Fc γ R11a RR and HH genotypes might be associated with autoimmune disorders and an adverse prognostic value in WM, whereas the prognostic value of the Fc γ R11a (V/F) polymorphism remains probably associated with the use of monoclonal antibody therapy only.