Cytogenetic abnormalities in Waldenström's macroglobulinemia

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The genetic bases of Waldenström Macroglobulinemia (WM) are poorly understood. Because of the difficulty in obtaining tumor metaphases for karyotype studies, few recurrent chromosomal abnormalities have been reported in WM. We have studied a cohort of 171 untreated WM patients, enrolled in a prospective randomized trial from the French Cooperative Group on Chronic Lymphocytic Leukemia and Waldenstrom Macroglobulinemia (FCG-CLL/WM), by conventional cytogenetic (CC) and Fluorescence *in situ* hybridization (FISH).
CC was systematically performed on bone marrow or peripheral blood, and FISH analysis carried out using 8 probes CEP4, CEP12, 13q14, 11q22 (ATM), 17p13 (TP53), IGH, BCL2 Abbott, 6q21 Q-Biogene, on metaphases and interphase nuclei.
The sex ratio was 2.1M/1F, the average age at inclusion was 66.9 years [40-89]. The mean percentage of lymphoplasmacytic cells was 53% [8-97]. Out of 140 / 171 successful CC, 65 (46.4%) showed clonal abnormalities. Out of 65 abnormal CC, 19 (29.2%) were complex, with more than or equal to three chromosomal

changes, and 22 (33.8%) showed translocations (balanced and unbalanced). Using CC and FISH, we observed 29/132 (22%) 6q deletion, 18/141 (12.8%) 13q14 deletion, 9/80 (11.2%) trisomy 18, 11/135 (8.1%) *TP53* deletion, 10/133 (7.5%) trisomy 4, 10/132 (7.6%) *ATM* deletion, 4/118 (3.4%) *IGH* rearrangement, and 4/136 (2.9%) trisomy 12.

Chromosomal abnormalities were compared to adverse characteristics described by Morel et al (ISSWM, blood 2009,113(8),4163-70) : advanced age (> 65 years), hemoglobin $\leq$ 11.5g/dl, platelet count $\leq$ 100x109/l, b2-microglobulin > 3 mg/l, and serum monoclonal protein concentration > 7g/dl. Patients with 6q deletion had significantly more frequently an albumin $\leq$ 3.5g/dl (15/29 (51.7%) *vs* 24/103 (23.3%), p=0.005), a b2microglobuline > 3 mg/l (20/29 (68.9%) *vs* 48/103 (46.6%), p=0.04). Similarly, patients with trisomy 4 had significantly more frequently a b2microglobuline > 3 mg/l (9/10 (90%) *vs* 59/123 (47.9%), p=0.02). Of note, all patients with trisomy 4 had a M-protein concentration > 2 g/dl (10/10 (100%) *vs* 73/123 (59.3%), p=0.02). Finally, there were significantly more patients with an age > 65 years, when *ATM* deletion was observed (9/10 (90%) *vs* 65/122 (53.2%), p=0.04).

Cytogenetic abnormalities in WM differ from those commonly reported in other B-cell neoplasms and confirm the originality of this disease. 6q deletion is frequent compared to chronic lymphocytic leukaemia (CLL) or marginal zone lymphoma (MZL) and 13q14 deletion is rare compared to CLL. In our series trisomy 12 is rare compared to atypical-CLL and MZL. Involvement of the *IGH* locus, which is frequent in multiple myeloma or lymphoplasmocytic lymphoma, is rare in WM. Finally trisomy 4 is present in WM but not reported in other B-cell malignancies.

The 6q deletion is the most frequent reported cytogenetic abnormality in WM. We found 22% cases with deletions of 6q21, a low percentage compared to the literature [38-54%]. This could be explained either by the difference in the used probe or by the absence of selection of lymphoplasmacytic cells before cytogenetic analyses. Another possibility is that our patients are untreated, and have been early analyzed in the course of the disease. Some of the chromosomal abnormalities are associated with classical adverse markers, in particularly the 6q deletion. Searches for correlations with clinical response are ongoing.