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Determining outcome in IgM gammopathies: integration of molecular, flow cytometry and clinical factors in an international, multicenter series (the SAL-TO study)

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Abstract

Background:

Waldenström macroglobulinemia (WM) is a rare, indolent B-cell lymphoproliferative disorder, often preceded by a history of IgM monoclonal gammopathy of undetermined significance (IgM-MGUS). WM progression mechanisms are not fully understood given the complex integration of clinical and molecular features.

Aims: To determine the impact of clinical, molecular and flow cytometry factors on overall survival (OS) and time to first treatment (TTFT) in a large, real life series of patients with IgM gammopathy.

Methods:

In this retrospective multicenter study, we collected real-life data on 577 patients with IgM gammopathy from 22 Spanish Centers. Moreover, 166 additional patients, treated at the University Hospital of Torino, Italy, were used as validation series. Multiparameter Flow Cytometry (MFC) and $MYD88^{L265P}$ evaluation (either by ddPCR or qPCR) were performed on baseline bone marrow (BM) samples in Salamanca and Torino laboratories respectively.

Results:

Overall median OS of the Spanish series was 126.7 months: 85.0 for symptomatic (sWM), 143.6 for asymptomatic WM (aWM), and 180.6 months for IgM-MGUS ($p<0.001$) respectively, while median TTFT for asymptomatic patients (aWM+MGUS) was 228.5 months, with 89% of pts remaining off treatment at 5 years. By multivariate analysis, significant clinical prognostic factors for OS included age > 65 years, male gender, diagnosis of sWM and beta-2-microglobulin >3, while age > 65 years, BM infiltration, hemoglobin <11.5 g/dl and platelets <100.000/mmc were associated with shorter TTFT.

Data from the Spanish and the Torino cohorts were pooled and divided into two groups based on high vs low baseline values of $MYD88^{L265P}$ Mut/WT ratio (cut-off point 0.162) and high vs low baseline MFC clonal B cell marrow infiltration (cut-off point 4.39%). By univariate analysis, the $MYD88^{low}$ group showed better OS ($p=0.005$, HR=0.44) and TTFT ($p=0.024$, HR=0.33) compared to the $MYD88^{high}$ group. Similarly, the MFC^{low} group had increased OS ($p=0.033$, HR=0.65) and TTFT ($p=0.008$, HR=0.37) compared to the MFC^{high} group. Moreover, by combining MFC and MYD88 baseline levels, patients were stratified into low, intermediate and high risk classes (LR: $MFC^{low}/MYD88^{low}$, IR: either $MFC^{low}/MYD88^{high}$ or $MFC^{high}/MYD88^{low}$; HR: $MFC^{high}/MYD88^{high}$). The high risk group significantly differed from the others in terms of OS (n= 156, $p=0.005$, HR=3.28, figure 1) and TTFT (n= 92, $p=0.003$, HR= 9.61), while the intermediate-risk group ($p=0.015$,

HR=4.76) was also significantly different from the low risk group for TTFT. Multivariable analysis confirmed a significant impact of MYD88 mutation and MFC baseline levels on both OS and TTFT. Finally, competing risk analysis showed, in the $MFC^{high}/MYD88^{high}$ group, a statistically significant increment in disease-related rather than unrelated deaths at 5 years (2.2% vs 19%, p=0.002, for $MFC^{low}/MYD88^{low}$ vs $MFC^{high}/MYD88^{high}$ respectively).

Conclusions: Our retrospective study shows that $MYD88^{L265P}$, by PCR quantitative analysis, and marrow infiltration, by MFC, play a significant prognostic role in OS and in the treatment indications in patients with IgM gammopathy. Prospective validation studies may greatly help to define prognostic tools for IgM gammopathy and to better define patients with high risk WM.

Figure 1: Overall survival based on MFC/MYD88 risk groups (Low risk vs Intermediate risk, vs High risk)