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

AUTHORS

Dogliotti Irene[1], Jiménez Cristina[2], Peri Veronica[1], Ferrante Martina [1], Musto Davide[1], Mercadante Silvio[1], Zaccaria Gian Maria[3], Ghislieri Marco [4], Benevolo Giulia[1], Ocio, Enrique María[5], Rubio Araceli[6], Murillo Ilda[6], Escalante Fernando[7], Aguilera Carmen[8], García Mateo Aránzazu[9], García de Coca Alfonso[10], Roberto Hernández[11], Dávila Julio[12], Cavallo Federica[1], Puig Noemi[2], González de la Calle Veronica[2], Maria Eugenia Sarasquete[2], Alcoceba Miguel [2], Ragaini Simone[1], Clerico Michele[1], Consoli Chiara[1], García-Álvarez María[2] Chillón María del Carmen[2], Medina Alejandro[2], González Díaz Marcos[2], Gutiérrez Norma Carmen[2], Bruno Benedetto[1], Drandi Daniela[1], Ferrero Simone[1] and García-Sanz Ramon[2]

INSTITUTIONS

1) Division of Hematology, Department of Biotechnology and Health Sciences, University of Torino, Italy;

2) Haematology Department, University Hospital of Salamanca, Research Biomedical Institute of Salamanca (IBSAL), CIBERONC and Center for Cancer Research-IBMCC (USAL-CSIC), Salamanca, Spain;

3) Department of Electrical and Information Engineering (DEI), Polytechnic University of Bari, Bari, Italy;

4) Department of Electronics and Telecommunications, Politecnico di Torino, Turin, 10129, Italy and PolitoBIOMed Lab, Politecnico di Torino, Turin, 10129, Italy;

5) Haematology Department, University Hospital of Marqués de Valdecilla, Santander, Spain;

6) Hematology Department, Hospital Miguel Servet, Zaragoza;

7) Hematology Department, Hospital Complex of León, León, Spain;

8) Hematology Department, Regional Hospital of El Bierzo, León, Spain;

9) Hematology Department, General Hospital of Segovia, Segovia, Spain;

10) Hematology Department, University Clinical Hospital of Valladolid, Valladolid, Spain;

11) Hematology Department, Virgen de la Concha Hospital, Zamora, Spain;

12) Hematology Department, Nuestra Señora de Sonsoles Hospital, Ávila, Spain.

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)