

The presence of $\geq 10\%$ bone marrow plasma cells at diagnosis is associated with shorter time to first treatment in patients with Waldenstrom's Macroglobulinemia: results from the observational prospective and retrospective BIO-WM study of Fondazione Italiana Linfomi

Emilia Cappello¹, Gianmarco Favrin¹, Daniela Drandi², Silvia Zibellini³, Luigi Marcheselli⁴, Veronica Peri², Irene Dogliotti⁵, Federica Cavallo⁶, Angela Ferrari⁷, Michele Merli⁸, Giulia Zamproga⁹, Luca Laurenti¹⁰, Simona Tomassetti¹¹, Emanuele Cencini¹², Giacomo Loseto¹³, Silvia Finotto¹⁴, Monia Marchetti¹⁵, Francesca Re¹⁶, Antonello Sica¹⁷, Jacopo Olivieri¹⁸, Chiara Varraso³, Cristina Jimenez¹⁹, Cristina Picone³, Noemi Puig¹⁹, Giulia Benevolo, Ramòn Garcia-Sanz¹⁹, Simone Ferrero², Marzia Varettoni³

1. Department of Molecular Medicine, University of Pavia, Pavia, Italy
2. Hematology, Department of Molecular Biotechnologies and Health Sciences, University of Torino, Italy
3. Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
4. Fondazione Italiana Linfomi, Clinical Trial Office, Modena, Italy
5. Stem Cell Transplant Unit, University Hospital AOU Città della Salute e della Scienza, Torino, Italy
6. Division of Hematology, A.O.U. Città della Salute e della Scienza di Torino, Torino, Italy
7. Ematologia, AO Arcispedale Santa Maria Nuova - IRCCS, Reggio Emilia, Italy
8. UOC Ematologia, Ospedale di Circolo e Fondazione Macchi – ASST Sette Laghi, Varese, Italy
9. SC Ematologia, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy
10. S. Ematologia, Dipartimento Scienze Radiologiche Radioterapiche ed Ematologiche, Fondazione Policlinico Universitario A Gemelli, Roma, Italy
11. Ematologia, Ospedale degli Infermi di Rimini, Rimini, Italy
12. U.O.C. Ematologia, AOU Senese, Siena, Italy
13. U.O.C Ematologia, IRCCS Istituto Tumori Giovanni Paolo II, Bari, Italy
14. Oncologia 1 - I.R.C.C.S., Istituto Oncologico Veneto, Padova, Italy
15. Ematologia, Ospedale Civile SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy
16. UO Ematologia e CTMO, Azienda Ospedaliera Universitaria di Parma, Parma, Italy
17. Oncologia Medica ed Ematologia, AOU Università degli Studi della Campania Luigi Vanvitelli, Napoli, Italy
18. Clinica Ematologica, Centro Trapianti e Terapie Cellulari "Carlo Melzi", Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy
19. Hospital Universitario de Salamanca (HUSAL), IBSAL, IBMCC (USAL-CSIC), CIBERONC, Salamanca, Spain

Background. Waldenstrom's Macroglobulinemia (WM) is a mature B-cell neoplasm characterized by bone marrow (BM) infiltration of lymphoid cells, lymphoplasmacytic cells and plasma cells (PC). The degree of differentiation toward plasma cells is highly variable from patient to patient. In a retrospective study an excess of PC at diagnosis was associated with a trend towards shorter time to next treatment and overall survival (Zanwar S et al, Blood 2019; 134; Supplement 1: 1532).

Aim. Here we analyzed patients enrolled in the multicentric observational prospective and retrospective BIOWM study of Fondazione Italiana Linfomi (FIL) with the aim to compare

clinical, biological features and outcomes of patients with WM based on the BM PC percentage at diagnosis.

Methods. Patients with WM were divided into 2 groups: those with <10% PC and those with ≥10% PC by immunohistochemistry (IHC) in the BM biopsy performed at diagnosis. Clinical characteristics and outcome of the two groups were compared. Patients for whom BM PC were not quantified were excluded from the analysis.

Statistical analysis. Continuous variables were compared using Mann-Whitney test and categorical variables were compared using Fisher's exact test. Time to first treatment (TTFT) was defined as the time between diagnosis and start of therapy. Progression-free survival (PFS) was defined as the time between diagnosis and progression (event) or death/last follow-up. Overall survival (OS) was defined as the time between diagnosis and death for any cause or last follow-up.

Results. Of 155 patients included in the analysis, 103 (66%) had less than 10% PC and 52 (34%) had ≥10% . Patients with ≥10% PC had higher levels of serum monoclonal protein (median 2.6 g/dL versus 1.1 g/dL, $P<0.001$) and more frequently had a serum beta2-microglobulin levels above the upper limit of normal (ULN). The proportion of patients harboring the MYD88^{L265P}, CXCR4 mutations or TP53 mutations was similar between the two groups (Table 1). Overall, 73 of 155 patients were treated, at diagnosis or after an initial "watch and wait" period. The proportion of patients needed therapy was significantly higher among patients with ≥10% PC as compared with patients with <10% PC (61% vs 40%, $P<0.001$). TTFT was significantly shorter in patients with ≥10% PC (median 16 months versus 42 months, $P=0.013$) (Figure 1). Rituximab and Bendamustine was the most common frontline treatment in patients with ≥10% PC (66%), whereas Dexamethasone+Rituximab+Cyclophosphamide (DRC) or DRC-like regimens were the preferred treatments in patients with <10% PC (61%) ($P<0.001$). No difference was observed in response rates between the two groups. Five-year PFS and OS were 80% and 85% respectively and were similar in the two groups.

Conclusions. Patients with ≥10% PC at diagnosis have higher levels of serum monoclonal component and a significantly shorter TTFT as compared with patients with <10% PC. In this study, patients with ≥10% PC more frequently received Rituximab and Bendamustine as frontline treatment, while DRC and DRC-like regimens were preferred in patients with <10% PC. The outcome was similar in the 2 groups.

Table 1. Baseline patients' characteristics

Variable	Patients with <10% BM PC	Patients with ≥10% BM PC	P value
Age >65 years (% of pts)	60	60	1.00
Males (% of pts)	59	62	0.864
LDH >ULN (% of pts)	12	18	0.457
Beta2-microglobulin >ULN (% of pts)	40	60	0.045
Serum monoclonal component >2 g/dL (% of pts)	26	65	<0.001
Bence-Jones proteinuria (% of pts)	47	61	0.130
Hemoglobin (g/dL), median (range)	12.5	11.9	0.055
Absolute lymphocyte count x10 ⁹ /L, median (range)	1.9 (1.5-2.6)	1.9 (1.4-2.3)	0.620
Platelets x 10 ⁹ /L, median (range)	242 (187-314)	247 (197-321)	0.726
MYD88 (L265P) mutation (% of pts)	96	90	0.313
CXCR4 mutation (% of pts)	22	27	0.540
TP53 mutation (% of pts)	3	8	0.425

Figure 1. Time to first treatment in WM patients according to the percentage of bone marrow plasma cells at diagnosis

