Prognostic factors in monoclonal gammopathy of undetermined significance

A retrospective evaluation of 285 patients with monoclonal gammopathy of undetermined significance was performed to identify variables associated with progression, actuarial progression free survival (PFS) and overall survival (OS). Three variables, level of uninvolved immunoglobulins (HR 4.98, CI95% 2 – 12.4, *p*=0.0006), monoclonal protein concentration (HR 4.04, CI95% 1.6–10.34, *p*=0.004), and erythrosedimentation rate (HR 3.94, CI95% 1.33–11.6, *p*=0.01), showed independent prognostic significance. With a median follow-up of 66 months (range 6–378), PFS and OS at 10 years were 89% and 91% respectively.

Haematologica. 2008 Jan; 93:(1)153-154. DOI: 10.3324/haematol.11744

Since a small percentage of patients with monoclonal gammopathy of undetermined significance (MGUS) will progress to a malignant disorder, periodic follow-up of these patients is warranted.[1] The strongest predictor for progression is the serum monoclonal component (MC) concentration.[2,3,4] Other prognostic factors mentioned in the literature are: type of MC,[2,5] level of uninvolved immunoglobulins (UI),[3,6] Bence Jones proteinuria,[3,6] light chain isotype,[4] erythrosedimentation rate (ESR),[6] percentage of bone marrow plasma cells[3,4,6] and serum kappa-lambda free light chain ratio.[7] More recently, it has been reported that proteomic microarray techniques could recognize MGUS with a positive predictive value of 98%.[8]

We performed a retrospective study of 285 patients with MGUS according to Kyle's definition[2] in our institution between 1982 and 2007, evaluating whether any simple hematologic parameter performed at diagnosis had prognostic value for progression. Other end-points were to determine the rate of progression, progression-free survival (PFS) and overall survival (OS). MC was detected by agarose gel and/or cellulose acetate electrophoresis in serum and/or urine. Identification of the MC was performed by immunoelectrophoresis or immunofixation, and quantification of immunoglobulins, by radial immunodifussion.

Patients with a MC >3 gr/dL and/or a bone marrow plasma cell infiltration >10%, or evidence of other lymphoproliferative disorder, such as non- Hodgkin's lymphoma (NHL) or chronic lymphocytic leukemia, were excluded. Patients with IgM monoclonal protein and unequivocal evidence of bone marrow infiltration by lymphoplasmacytic lymphoma (i.e. >10% of lymphoid cells in bone marrow, <10% with clonal disease demonstrated by flow cytometry) were considered to have Waldenstrom´s Macroglobulinemia (WM)[9] and were not included in our study.

Progression to myeloma was defined by: MC >3 gr/dL, plasma cell bone marrow infiltration >10%, or associated lytic bone lesions. Progression to another B-cell neoplasm was considered when there was histologic evidence of the disease.

PFS and OS were evaluated for patients with a minimum 6 month or longer follow-up, and calculated using the Kaplan-Meier test. The effects of potential risk factors on progression rates were examined in a Cox proportional-hazard model.

Patients' characteristics are shown in Table 1. Two hundred and sixty-eight patients (93%) remained in stable condition with a median follow-up of 66 months (range 6-378). Twenty-one patients progressed (7%): 16 to myeloma (76%), 2 to NHL (10%), 2 to WM (10%) and 1 to amyloidosis (4%). During the study, 14 patients died (5%): 2 related to disease progression (14%), 9 due to other disorders, such as cardiovascular disease or other malignancies (64%) and 3 of unknown causes (21%). The PFS and OS at 10 years were 89% and 91% respectively (Figure 1).

Table 1. Patients' characteristic (n=285).

Variable		*N. (%)*	*median*	*range*
Gender	Male	109 (38)		
	Female	176 (62)		
Age (years)	< 50	55 (19)	44	24-49
	≥ 50	230 (81)	64	50-87
[MC] (gr/dL)	0.1-1	224 (79)	0,5	0.1-1
	1.01-3	61 (21)	1.5	1.01-2.85
Type of monoclonal component	IgG	205 (72)		
	IgA	42 (15)		
	IgM	34 (12)		
	Biclonal	4 (1)		
Type of light chains	κ	136 (48)		
	λ	79 (28)		
	Not evaluated	70 (24)		
Bence Jones	Negative	193 (68)		
	Positive	26 (9)		
	Not evaluated	66 (23)		
Level of UI	Normal	227 (80)		
	Reduced	58 (20)		
Plasma cells in bone marrow (%)	≤ 5	38 (13)	2	0-4
	> 5	28 (10)	7	5-10
	Not evaluated	219 (77)		
Albumin (gr/dL)	Normal (≥3.5)	247 (87)	4	3,5-4,7
	Reduced (<3.5)	38 (13)	3.4	2.41-3.49
β^2 microglobulin (ng/L)	Normal (≤2.5)	98 (34)	1,7	0.36-2,5
	Elevated (>2.5)	90 (32)	3.5	2.6-39
	Not measured	97 (34)		
ESR (mm/h)	Normal (≤15)	120 (42)	9	2-15
	Elevated (>15)	165 (58)	28	16-130

MC: monoclonal component, UI: uninvolved immunoglobulins; ESR: erythrosedimentation rate.

The level of UI (HR 4.98, CI95% 2-12.4, *p*=0.0006), MC concentration (HR 4.04, CI95% 1.6-10.34, *p*=0.004) and ESR (HR 3.94, CI95% 1.33-11.6, *p*=0.01) were independent predictors of progression when analyzed according to Cox's proportional hazard model.

The rate of progression in our experience (7%, median follow-up 66 months) is similar to that published by Kyle *et al.*[2] (8%, median follow-up 185 months) and Baldini *et al.*[5] (6.8%, median follow-up 70 months), and slightly higher than that described by Cesana *et al.*[8] (5.8%, median follow-up 65 months). The PFS (89% at 10 years) is also similar to the data reported by Kyle[2] (90% at 20 years), although not strictly comparable, due to their longer follow-up and higher number of patients.

According to previous publications, age, gender, hemoglobin level, β_2 microglobulin, albumin and light chain isotype have no prognostic value for progression.[2,3,6] As the level of UI, MC concentration and ESR were independent predictors of progression, they could identify a higher probability of malignant evolution in patients with MGUS. These variables have already been

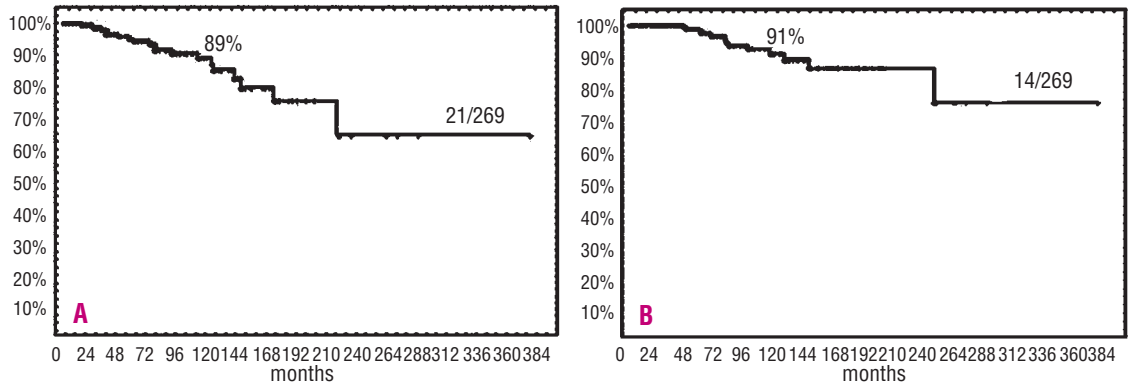

Figure 1. (A) Progression Free Survival (PFS) of the patients with MGUS (89% at 10 years). (B) Overall Survival (OS) of the patients with MGUS (91% at 10 years)

described by others.[2,3,6]

Bone marrow biopsy should be performed in patients with high-risk MGUS (MC >1 gr/dL, reduced UI and elevated ESR) or if any other feature suggests the presence of myeloma or other malignancy. Microarray studies to detect genetic expression in these patients will probably soon lead to a better understanding of this disease.

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Acknowledgments: we thank Graciela Enrico for the manuscript's grammatical corrections, Mariana Juni for the initial organization of the study and statistical analysis and Dante Intile for the statistical analysis.

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