Serum-free light chain elevation is associated with a shorter time to treatment in Waldenstrom's macroglobulinemia

Waldenström's macroglobulinemia (WM) is a rare low-grade lymphoproliferative disorder of the elderly[1] with an indolent course but a highly variable prognosis.[2-4] Recently, an international prognosis scoring system for WM (IPSS) was developed from the largest retrospective series of WM patients, based on independent factors of adverse prognosis (age >65 years, platelet count ≤100×10^9/L, β2-m >3 mg/L, M-protein >7.0 g/dL, Hb ≤11.5 g/dL and albumin ≤3.5 g/dL).[5]

A serum immunoassay was recently developed for circulating free immunoglobulin light chains (FLC)[6] and has proved very useful for managing light chain myeloma and AL amyloidosis. The possible usefulness of FLC assay in WM has not been evaluated. We conducted a retrospective study of 42 patients diagnosed with WM in our institution who had at least one serum FLC assay prior to any treatment.

The baseline evaluation was performed an average of six months after diagnosis (range 0–71 months), and the median follow-up was 24 months (range 2–72 months). Twenty-eight patients started treatment during the follow-up period, based on international criteria for treatment initiation.[3] The time to treatment (TTT) was defined as the time between the baseline FLC assay and the date of treatment initiation. All the patients had a baseline evaluation that included a detailed physical examination, peripheral blood cell counts, kidney function tests, serum protein electrophoresis, and serum β2-microglobulin assay (β2-m). Prognostic factors were tested by using the cut-off values of the IPSS for WM.[5]

Serum free light chain was assayed with the Freelite® kit (The Binding Site Ltd, Birmingham, UK). The analysis was restricted to the absolute value of involved FLC, corresponding to the isotype of the monoclonal IgM. The study was approved by the local ethics committee.

Correlations between continuous variables and dichotomized or other continuous variables were identified with Wilcoxon's test and Pearson's test respectively. Variables with p values below 0.10 in bivariate analyses were entered into a Cox multiple regression model. All tests were two-sided and were performed with R 2.4.1 software. The baseline characteristics of the 42 patients are summarized in Table 1. Twenty-eight patients (67%) were symptomatic at baseline FLC evaluation. None had light chain amyloidosis. Only one patient had severe chronic renal failure. The level of the involved FLC was elevated in 83% of the patients.

When analyzed as continuous variables, the FLC and monoclonal component levels were not related to each other (p=0.89), as previously shown in multiple myeloma,[7] possibly reflecting defective co-ordinated immunoglobulin synthesis. In univariate analysis (Table 1), the FLC level, expressed as a continuous variable, was higher in patients with β2-m >3 mg/L (p=0.03) or with albumin <35 g/L (p=0.04). Symptomatic patients also had significantly higher FLC values (p=0.037). In multivariate analysis (Table 1), a β2-m level >3 mg/L (median FLC value=66.8 mg/L *vs.* 32.0 mg/L if β2-m <3 mg/L, p=0.018) and a symptomatic disease both correlated with the FLC value (median FLC value=59.4 mg/L *vs.* 32.0 mg/L if asymptomatic, p=0.046).

Altogether, our results show that FLC elevation is frequent in WM, that FLC level is not simply a surrogate of the M-component value and correlates with prognostic factors reflecting the tumor burden such as β2-m level and albumin concentration, both of which have independent prognostic significance in WM.[2,4] In univariate analysis (Table 2), the FLC level, expressed as a continuous variable, influenced the time to treatment (p=0.006) in the overall cohort (symptomatic and asymptomatic patients), as did the monoclonal component level (p<0.001), the albumin level (p=0.02), anemia

Table 1. Patients' characteristics and correlations with free light chain values.

	N or median	*% or range*	*Correlation with FLC (univariate p value)*	*Correlation with FLC (multivariate p value)*
Patients	42			
Sex (M/F)	24/18	57%/43%		
Age at presentation (yrs.)	61.8	36.7-83.2		
Age > 65 years	18	43%	0.38	
Light chain isotype κ	36	86%		
Follow-up (months)	24.1	2.3-72.0		
First treatment during follow-up	28	67%		
Time to treatment (months)	14	0–1201		
Symptomatic WM	28	67%	0.037	0.046
Serum M-spike (g/L)	17.0	8.2-62.6	0.89	
Hemoglobin (g/dL)	11.7	6.4-15.7		
Hb <11.5 g/dL	19	45%	0.12	
Platelets (g/L)	240	79-594		
Platelets <100 g/L	3	7%	0.09	NS
Albumin (g/L)	42.6	23.5-53.6		
Albumin <35 g/L	5	12%	0.04	NS
β2-m (mg/L)	2.8	1.2-6.3		
β2-m >3.0mg/L	12	29%	0.03	0.018
Serum creatinine (μmol/L)	85	51-579		
FLC (mg/L)	48.6	11.3-19400.0		
FLC > N	35	83%		
FLC >80 mg/L	12	29%		
Abnormal FLC ratio	31	74%		

Table 2. Prognostic value of biological values for time to treatment (*p values).

	*Univariate analysis**	*Multivariate analysis**	*Hazards ratio (95% CI)*
FLC	0.006	0.02	1.003* (1.001-1.01)*
Serum M-spike	<0.001	< 0.001	1.07 (1.028-1.11)
Age >65	0.85		
Hb <11.5 g/dL	0.004	0.79	
Platelets <100 g/L	0.02	0.5	
β2-m >3 mg/L	0.49		
Albumin <35 g/L	< 0.001	0.02	4.0 (1.178-13.71)

**HRs are indicated for increases of 20 mg/L in absolute involved FLC value.*

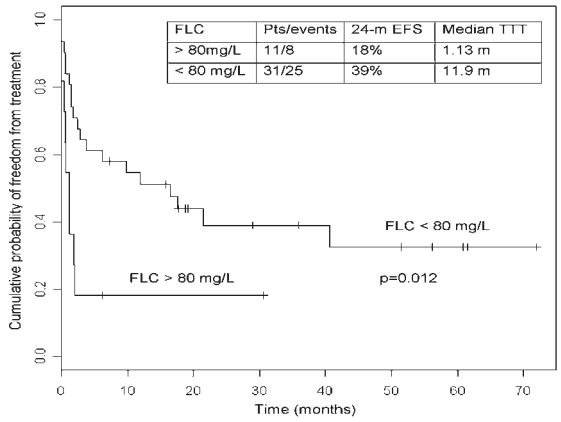

Figure 1. Time to treatment according to baseline involved free immunoglobulins light chains value.

value (p=0.02, HR=1.00), the monoclonal component level (p<0.001, HR=1.07), and the albumin level (p=0.03, HR=4.0). The FLC value correlates with TTT in part because symptomatic patients, who receive treatment at diagnosis,[3] have higher FLC values than asymptomatic patients (median FLC value 59.4 mg/L *vs.* 29.4 mg/L, p= 0.037). However, the correlation between TTT and FLC persisted in the subgroup of asymptomatic patients (p=0.047). Factors predictive of the time to treatment are of great value to clinicians. The few studies that have addressed this issue in WM[8–10] identified the following predictors: anemia,[8,9] β2-m >3.0 mg/L,[9] IgM peak >3.0 g/dL[8] and 6q deletion.[10]

Our results show that the FLC value, when expressed as a continuous variable, correlates negatively and independently with the time to treatment: for instance, treatment starts a median of one year after diagnosis if the FLC value is over >80 mg/L. If confirmed in larger, prospective studies, FLC monitoring in WM patients may be warranted.

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Key words: Waldenstrom's macroglobulinemia, serum-free light chain, time to treatment, prognosis.

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