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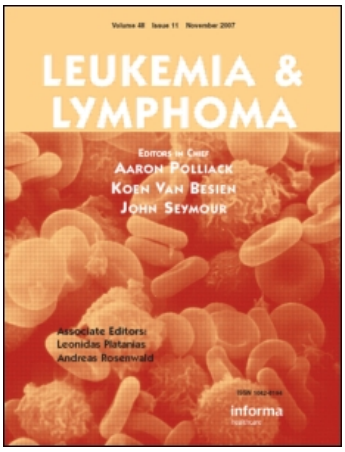

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Serum immunoglobulin free light chain correlates with tumor burden markers in Waldenstrom macroglobulinemia

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Abstract

The serum IgM level has been utilised as a marker of tumor progression and to assess response to therapy in patients with Waldenstrom macroglobulinemia (WM). However, there are many limitations to the IgM protein level. The objective of this study was to evaluate the association of known tumor burden markers and prognostic factors with serum free light chain (sFLC) in 98 patients with WM. We demonstrated that sFLC measurement accurately differentiated IgM-MGUS compared with WM reflecting a measurement of tumor burden. In univariate and multivariate analysis, median sFLC at the cut-off at 60 mg/L was higher for WM patients with low hemoglobin and high β2M, when we applied the WM-IPSS cut-offs, but showed no association with IgM level. This study demonstrates that sFLC is a new marker in WM disease. Further analysis is required to prospectively study the role of sFLC in monitoring response to therapy and as a prognostic marker in WM patients.

Keywords: *Waldenstrom macroglobulinemia, serum-free light chain, tumor burden marker*

Introduction

The accurate diagnosis of Waldenstrom macroglobulinemia (WM) is difficult in some cases, due to the ill-defined overlap between IgM-monoclonal gammopathy of undermined significance (IgM-MGUS), asymptomatic and symptomatic WM. The serum IgM level has been utilised as a marker of tumor progression and to assess response to therapy in WM [1]. However, there are many limitations to the IgM protein level. The prognostic significance of the IgM level at diagnosis remains controversial in WM [2,3]. In addition, the IgM level lacks sensitivity to early response of therapy and early relapse especially due to its prolonged half-life. Therefore, the serum IgM level does not reflect in a sensitive and accurate fashion the tumor burden or prognosis in WM, and there is a need to identify serum markers that reflects tumor burden in WM and correlate with the outcome of these patients.

The Freelite assay is a new and sensitive immunoassay that measures serum immunoglobulin free light chains levels [4]. The sFLC assay has shown

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significant clinical application in plasma cell dyscrasias, specifically in MM, primary systemic amyloidosis and MGUS [5]. In MM, it is used to monitor response to therapy especially in patients with oligo-secretory or non-secretory MM [4] and is also now included in the new response criteria for MM [4,6] based on its sensitivity to assess lower tumour burden compared with serum protein electrophoresis. The presence of an abnormal FLC ratio is a significant predictor of progression in MGUS patients [7], and also predicts early progression of disease compared with other tumor markers in MM [8]. The objective of this study was to evaluate the association between known tumour burden markers and prognostic factors with sFLC in patients with WM.

Patients and methods

This study was performed through an international collaboration of Dana-Farber Cancer Institute, Boston, MA, and Hopital Huriez, CHRU, Lille, France. A total of 162 patients with WM ($N=98$) or IgM-MGUS ($N=68$) were studied. Of these, 101 patients were tested at Dana-Farber Cancer Institute, and 69 patients at Hopital Huriez. The diagnosis of WM was according to the recommendations [9]. Patients who had an IgM M-component with absence of lymphoplasmacytic cells involvement in the bone marrow, except for two asymptomatic patients whose bone marrow was not performed and whose serum IgM levels were 200 and 500 g/L [9]. All patients gave informed consent. Approval for the review of these records was obtained from the Dana-Farber Cancer Institute and Hopital Huriez Institutional Review Boards and was in accordance with the Declaration of Helsinki.

The serum-free κ and λ light chain levels were measured using the serum-free light chains assay (The Binding Site, UK) [10]. The clonal FLC was considered the involved immunoglobulin FLC (sFLC) in order to pool the data of the monoclonal κ and λ patients for the purpose of the analyses [11].

Statistical analysis

To describe the distribution of sFLC, the median, interquartile range (IQ range) are reported. Median values are compared using Wilcoxon rank-sum test. Fishers's exact test was used to compare proportions. To adjust for multiple variables in a model, a logistic regression model was used to evaluate the association between dichotomised sFLC and known tumor burden measures or prognostic factors. The odds ratio (OR) and the 95% confidence intervals (CI 95%) are reported. All statistical tests are two-sided. All analyses were conducted using SAS v8 software.

Results and discussion

Patient characteristics

Patient characteristics are described in Table I for the 166 patients. In the patients with WM, 38 (39%) received prior therapy with a median duration from last therapy to sFLC collection of 1 year (range, 6–30 months). The treated patients received either alkylating agents ($N=30$) or fludarabine ($N=25$) with or without rituximab.

sFLC level is significantly different between IgM-MGUS and WM patients

The median (IQ range) sFLC in IgM-MGUS was significantly lower than for WM patients [20 mg/L (16–33) vs. 36 mg/L (16–140), $p=0.0003$]. Median sFLC was similar for previously treated and untreated patients. In this study, we demonstrated that sFLC accurately differentiated patients with IgM-MGUS compared with those with WM reflecting an assessment of tumor burden and we identify sFLC measurement as a new tumor burden marker. In our study, 76.5% and 23.5% of patients with WM and IgM MGUS had abnormal κ/λ sFLC ratio, respectively ($p<0.001$). The sFLC κ/λ ratio values correlated well with involved sFLC levels ($r=0.602$; $p<0.001$). Interestingly, sFLC values

Table I. Patient characteristics.

Characteristic	WM ($N=98$)	IgM-MGUS ($N=68$)
Age (years)		
>65 (N [%])	40 (41)	25 (39)
Median (range)	63 (37–90)	62 (39–85)
	N %	N %
Males	56 (57)	44 (69)
κ Light chain	75 (77)	51 (80)
Hepatosplenomegaly	4 (4)	0 (0)
Hemoglobin (g/dL)*		
<10	16 (17)	2 (3)
≤11.5	31 (32)	7 (11)
WBC ($<4\times10^9$/L)	14 (14)	3 (5)
Platelets ($<100\times10^9$/L)	9 (9)	0 (0)
IgM (g/L)*		
>40	16 (16)	0 (0)
>70	4 (4)	0 (0)
β2m (>3 mg/L)*	35 (36)	7 (11)
Serum viscosity (≥1.8 cp)	39 (70)	2 (50)

Degree of significance, *$p<0.001$. Serum viscosity is present for 56 of the WM and 4 of the IgM-MGUS patients.

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measurement was lower in WM compared with MM, overall [4,12,13].

sFLC correlates with markers of high tumor burden and adverse prognosis in WM

We then investigated whether high sFLC level is correlated to poor prognostic indicator in patients with WM. We could not evaluate the role of sFLC level on overall survival given the short follow-up in this series and the long survival of patients with WM. We categorised the variables studied in this series according to cut-offs recently proposed in the International Prognostic Scoring System for WM (IPSS) [2], and previously published markers including hemoglobin (<10g/dL), WBC ($<4\times10^9$/L), serum IgM (>40 g/L) and serum viscosity (>1.8 cp) to separate patients with markers of high tumor burden and poor prognosis [14,15]. In our series, 45 (46%), 36 (37%) and 17 (17%) patients with WM had low, intermediate and high risk in the WM-IPSS scoring system, respectively. The median (mg/L, IQ range) sFLCs were 32 (16–76), 37 (16–124) and 95 (39–288), respectively ($p=0.05$). Median sFLC levels were significantly higher ($p\leq0.05$) in patients with higher tumor burden (serum viscosity ≥1.8 cp, IgM level >40 g/L, and hemoglobin <10 g/dL or ≤11.5 g/dL) and with adverse prognosis markers (β2M >3 mg/L). Median sFLC was marginally higher ($p=0.07$) for the WM patients with hepatosplenomegaly as compared with those without. In our study, high serum IgM levels correlated well with markers of high tumor burden and of poor prognostic impact. We also found that high sFLC levels were associated with increase serum IgM (greater than 40 g/L) level, consistent with the positive correlation also observed with markers of high tumor burden and of poor prognostic impact, such as high β2-microglobulin and a higher WM-ISS score [2].

sFLC level higher than 60 mg/L is strongly associated with markers of adverse prognosis

In order to use the sFLC level measurement in clinic and to identify patients with WM, we sought to determine a cut-off value that would distinguish patients with WM from those with IgM-MGUS, and identify patients with poor prognosis markers. The upper 95th percentile (60 mg/L) of the IgM-MGUS patients was used to establish a cut-off value for sFLC. Using this cut-off, the sFLC for WM was dichotomised as low (≤60 mg/L) vs. high (>60 mg/L). As shown in Table II, the group of patients with higher sFLC levels had significantly higher percentage of patients with high β2m and IgM levels, and low hemoglobin levels as compared with those with sFLC ≤60 mg/L. The sFLC was elevated for all four patients with clinical hepatosplenomegaly. No difference was detected by prior treatment.

Table II. Characteristics of Waldenstrom macroglobulinemia patients with sFLC level ≤60 mg/L ($N=59$) compared with >60 mg/L ($N=39$).

Characteristic	sFLC ≤60 mg/L, N (%)	sFLC >60 mg/L, N (%)	Fisher's p-value
λ Light chain	12 (20)	11 (28)	0.47
Hepatosplenomegaly	0 (0)	4 (10)	0.02
Age (>65 years)	23 (39)	17 (44)	0.68
Hemoglobin (g/dL)			
<10	6 (10)	10 (26)	0.05
≤11.5	11 (19)	20 (51)	0.0009
WBC ($<4\times10^9$/L)	7 (12)	7 (18)	0.56
Platelets ($<100\times10^9$/L)	5 (9)	4 (10)	0.99
IgM (g/L)			
>40	3 (5)	13 (33)	0.0004
>70	1 (2)	3 (8)	0.30
β2M (>3 mg/L)	12 (20)	23 (59)	0.0002
Serum viscosity (≥1.8 cp)	20 (34)	19 (49)	0.14
Previous treatment	23 (39)	15 (38)	0.99

sFLC, involved serum-free light chain; β2M, β2 microglobulin. The reference range for κ is 3.3–19.4 mg/L; for λ is 5.7–26.3 mg/L. Serum viscosity is present for 56 of the WM.

In the logistic regression model, factors evaluated for association with high sFLC were age (>65 years), hemoglobin (<10 g/dL or ≤11.5 g/dL), platelet count ($<100\times10^9$/L), WBC ($<4\times10^9$/L), β2M (>3 mg/L), M-protein (>40 g/L or >70 g/L). Modelling results showed a significant association of sFLC with elevated β2M [OR = 3.9, (CI 95% 1.4–11.1); $p=0.009$), and anemia [OR = 3.5, (CI 95% 1.1–11.4), $p=0.04$], but not IgM level, when we applied the WM-IPSS cut-offs.

In summary, we demonstrate that sFLC differentiates patients with IgM-MGUS from those with WM. It is related to poor prognostic markers that isolate WM patients with progressing disease who require therapy. Future studies are needed to determine the value of sFLC on survival and to monitor response to therapy. These findings have therapeutic implications in the management of patients with WM.

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