The difference of free light chains as a predictor of kidney damage in patients with Multiple Myeloma

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ABSTRACT

Background: Multiple myeloma (MM) is a malignant neoplasm characterized by the clonal expansion of plasma cells that can release monoclonal immunoglobulins (monoclonal component) or part of theme. Since 2001, the k and λ serum free light chains (sFLC) evaluation and their ratio (rFLC) have made up the laboratory analysis more sensitive and precise in MM patients. The role of rFLC has been widely studied and discussed and now it is validated in the literature. Instead, the value of free light chains difference (dFLC), especially in MM is less known yet. The aim of this study is to evaluate the relationship between the dFLC and the kidney damage parameters in patients with MM, in comparison with the rFLC value.

Methods: We conducted a retrospective population-based study on 58 MM patients and we individuated two groups obtained considering the measures of dFLC and rFLC in relation to abnormal and normal values of some renal function markers, such us Bence-Jones proteinuria (BJ), albuminuria, proteinuria and serum creatinine. The Mann-Whitney test was used to test the difference between two independent samples.

Results: We observed a significant greater mean score of dFLC in patients with abnormal levels of BJ (2322.91>297.47, p=0.0001), albuminuria (2650.61>671.37, p=0.0016) and proteinuria (2327.19>593.14, p= 0.0025), while there was no significant difference for serum creatinine (1636.18<1870.85, p=0.994). Instead, no differences were observed for the rFLC parameter.

Conclusion: The data obtained allow us to conclude that dFLC can be considered a potential predictor of renal damage in MM patients, even better than rFLC.

Key words: Multiple Myeloma, free light chains difference, free light chains ratio, renal damage

INTRODUCTION

Multiple myeloma (MM) is a hematologic malignancy characterized by a monoclonal expansion of plasma cells [1-3]. Advances in medicine and the introduction of "new" drugs have allowed an improvement in the patients survival, although MM remains an incurable disease to date [4]. The occurrence of MM is consistently preceded by two precursor states: a pre-cancerous condition called gammopathy of undetermined significance (MGUS) and the asymptomatic clonal plasma cell disorder called Smoldering Myeloma (SMM) [5, 6].

Among clinical features, kidney damage is a common complication of MM; it is present in almost 50% of patients at the time of diagnosis and it is related to an increase in mortality [7-10]. Depending on the severity of the kidney injury, there may be a frank, irreversible and/or progressive damage in up to 50% of cases [11-14]. Multiple pathogenetic mechanisms may contribute to renal dysfunction in MM patients, but the most studied are those induced by the nephrotoxicity of monoclonal Ig and/or its components. [15-19].

A complete initial diagnostic workup is essential in the clinical management of MM patients and the serum free light chains (sFLC) represent a very sensitive and precise laboratory evaluation parameter [20-24]. For this reason, the sFLC evaluation is currently recommended by various international guidelines, such as International Myeloma Working Group (IMWG), The National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO), International Kidney and Monoclonal Gammopathy Research Group (IKMG) [25-30]. The only sFLC assay now accepted by FDA (Food and drug Administration) and recommended by the current guidelines is the Freelite® test (The binding Site, UK) [25].

The sFLC evaluation is mainly performed in terms of ratio between κ e λ chains (rFLC) and, sometimes, the difference between involved and uninvolved chains (dFLC).

As established by Katzmann et al., the reference range for sFLC kappa is 3.3-19.4 mg/L, for sFLC lambda 5.7-2.3.3 mg/L. The reference range for rFLC is 0.26-1.65 [31, 32].

To date, the role of rFLC has been widely studied and discussed and now it is validated in the literature; instead, the value of dFLC, especially in multiple myeloma is less known yet [33].

For this reason, we conducted a retrospective population-based study aimed at evaluating the dFLC parameter in MM patients, especially in those with alterations of kidney function, as dFLC could be more sensitive in assessing the light chain burden often responsible for severe kidney damage.

This analysis could be of great help in the clinical management of patients with MM and it could be also very useful in patients with the above mentioned precursor states of MGUS and SMM, in order to prevent clinical problems related to renal function.

METHODS

Population

The study sample was represented by 58 consecutive patients with new diagnosis of MM between April 1 2017 and September 30 2019. All patients were followed in the Hematology Division of the AOUP "P. Giaccone" of Palermo". Patients with IgA, IgG and Light Chain Mutliple Myeloma (LCMM) aged over 18 years were included.

Patients with liver cirrhosis, with another type of concomitant neoplasm or with another diagnosis of tumor disease made in the two prior years to hypothetical enrolment were excluded.

The sFLC was assayed with a nephelometric method using the Freelite® kit (The binding Site) on the BN ProSpec nephelometric system. The values relating to the dosage of sFLC kappa, FLC lambda, and dFLC were evaluated at baseline, before starting of the therapy program

Clinical and laboratory data concerning the patient's characteristics and blood disease, also essential for assessing the patients eligibility, were collected through the consultation of medical records. The study was conducted in accordance with the Declaration of Helsinki guidelines and the Ethics committee of the Hospital of the University of Palermo (date of approval 14/11/2018, report N°10/2018).we

Specific written informed consent was requested from the patients, in accordance with institutional and national requests, for the processing of personal data and above all for carrying out the planned biological investigations

The laboratory part of the study, especially in relation to the dosage of sFLC and other clinical parameters was conducted at the analysis laboratory "CORELAB" of the AOUP "P. Giaccone" Hospital of Palermo.

Statistical analysis

Data were presented as number and percentage for categorical variables, and continuous data were expressed as mean ± standard deviation (SD), unless otherwise specified. To individualize the renal dysfunction we considered two parameters as possible predictors, such as rFLC, and dFLC. For this scope we considered two Groups, called 1 and 2, for every parameter connected to renal dysfunction and considered in this study such as Bence-Jones proteinuria (BJ), albuminuria, serum creatinine and proteinuria score. The Group 1 was selected considering the rFLC and dFLC values associated to abnormal value of the above-mentioned parameters, while the Group 2 was selected, considering the rFLC and dFLC values associated to normal value of the same parameters. The abnormal and normal status was defined according to normal range of the parameters connected to renal dysfunction, as reported in Table 1. The Mann-Whitney test

was used to test the difference between two independent samples (Group 1 and 2). It was the alternative for the independent samples t-test, when the distribution of the samples is not Normal. Finally all tests with p-value (p) <0.05 were considered significant. The statistical analysis was performed using the Matrix Laboratory (MATLAB) analytical toolbox version 2008 (MathWorks, Natick, MA, USA) for Windows at 32 bit.

RESULTS

In our study we collected data from 58 patients with new diagnosis of MM, followed in the Hematology Division of the AOUP "P. Giaccone" of Palermo. The study sample was composed by 46.55% (27/58) of females and 53.45% of males (31/58), with ages into range 43-91, mean 70.60 y.o. and standard deviation 9.65 y.o. In relation to isotype, the study population includes: 22 patients with IgG k MM, 10 patients with IgG λ MM, 8 patients with IgA k MM, 8 patients with IgA λ MM, 3 patients with k LCMM and 7 patients with λ LCMM. In relation to the staging, 2/58 (3.5%) patients had ISS I, 13/58 (22.4%) had ISS II and 43/58 (74.1%) had ISS III.

In Table 1 we reported all parameters considered at baseline of this study. Particularly for some parameters we reported both mean ± standard deviation and the percentages of patients with abnormal score.

Tables 2 shows the statistical tests performed in this study. Particularly, we considered the measures of dFLC and rFLC divided of all patients, dividing them into Groups 1 and 2 according to abnormal or normal score respectively of parameters such as BJ, albuminuria, serum creatinine and proteinuria.

For every parameter it resulted rejected the normality hypothesis, therefore the Mann-Whitney test was used. Specifically, we observed a significant greater mean score of dFLC for Group 1 respect to Group 2, connected to BJ (2322.91 > 297.47, p=0.0001), albuminuria (2650.61>671.37, p=0.0016) and proteinuria (2327.19>593.14, p= 0.0025), while there was no significant difference for serum creatinine (1636.18<1870.85, p=0.994). Instead, no significant difference about mean score of rFLC there were between Group 1 and 2 connected to BJ (283.84> 43.22, p= 0.84), albuminuria (320.77>89.93, p=0.60), proteinuria (274.11>97.80, p=0.63) and serum creatinine (157.77<297.83, p=0.93).

DISCUSSION

In recent years, laboratory tests in the context of MM have increasingly been enriched with accurate tools, characterized by a high diagnostic and prognostic power. The sFLC evaluation represents one of the most important among theme and it has become essential for a correct and complete evaluation of patients. In fact, sFLC represent an important independent risk factor, since they are directly related to the tumor load. For this reason, since 2014, the ratio between the involved free light chain and the one not involved has been included by the IMWG among the MDEs (myeloma defining events). Specifically, the rFLC involved/uninvolved ≥ 100, with an involved chain size greater than 100 mg/L is among the malignancy biomarkers (SLiM criteria), considered an important criterion for deciding the beginning of an anti-MM treatment [1].

However, if in the literature there are more and more data relating to the clinical impact of the value of the individual FLCs and their ratio [34, 35], to date, not much data has been produced about dFLC parameter, especially in relation to the kidney damage in MM patients.

For this reason, we evaluated possible association between dFLC and some variables such as serum creatinine, BJ, albuminuria and proteinuria, all potentially associated with kidney damage. This research has shown a statistically significant correlation with almost all these parameters, when altered. Specifically, statistically significant correlations were observed with BJ, albuminuria e proteinuria, all parameters related to renal impairment. Instead, no correlation emerged with serum creatinine. In our opinion, from this analysis emerge the potential role of dFLC as a predictor of renal damage in MM patients. In fact, dFLC would be able to identifying specific renal alterations before the serum creatinine increase, full sign of kidney damage.

The aforementioned correlations have not been observed for the rFLC parameter that, while maintaining its important role, in this case is not able to predict a renal dysfunction.

CONCLUSION

In recent years, the high diagnostic and prognostic power related to the sFLC dosage evaluation in MM has led to consider this laboratory investigation as an important tool for the diagnosis, prognosis and the response assessment of patients.

The data obtained allow us to conclude that dFLC can be considered a good indicator of renal damage in MM patients, even higher than the value of rFLC.

This observation is fundamental because it allows a more specific assessment of renal damage in MM, and, in the same time, it would allow a prediction of possible renal damage in the context of MGUS and SMM, thus promoting a more accurate clinical monitoring in preclinical stages of MM.

Due to the sample size, we considered this study as preliminary analysis to detect a possible role of dFLC as predictor of renal dysfunctions in MM patients. Therefore,

TABLE 1. General characteristics of 58 participants at baseline

PARAMETERS	MEAN/ PERCENTAGE
Gender (M)	53.45% (31/58)
Age (years)	70.60±9.65
Age at diagnosis (months)	25.25±31.09
Beta2-microglobulin (normal range: 0.8-2.2)	7.94±7.18
% Abnormal	96.55% (56/58)
Hb (normal range: F=12-16/ M=12-18)	10.36±1.98
% Abnormal	77.59% (45/58)
PLT (normal range: 150000-450000)	193426.88±113658.44
% Abnormal	31.03% (18/58)
Serum calcium (normal range: 8.6-10.2)	9.57±1.45
% Abnormal	32.76% (19/50)
MC (normal range: <3g/dl)	3.11±2.06
% Abnormal	51.72%(30/58)
LDH (normal range: 50 U/l -250 U/l)	199.50±113.46
% Abnormal	20.69% (12/58)
Serum creatinine (normal range: 0.51 mg/l -0.95 mg/l)	1.40±1.45
% Abnormal	60.34% (35/58)
Proteinuria (normal range: 0.0 mg/l -150 mg/l)	616.83±964.86
% Abnormal	65.52% (38/58)
Albuminuria (normal range: <20 mg/l)	87.85±144.48
% Abnormal	53.45% (31/58)
Bone marrow plasma cells (abnormal value: ³10% mg/l)	47.88±25.44
% Abnormal	100% (58/58)
IgA (normal range: 70 mg/dl -400mg/dl)	1177.03±2106.34
% Abnormal	93.10% (54/58)
IgG (normal range: 700 mg/dl -1600mg/dl)	2566.71±2382.17
% Abnormal	91.38% (53/58)
IgM (normal range: 40 mg/dl -230mg/dl)	26.74±34.31
% Abnormal	86.21% (50/58)
MM isotype	
IgG k MM	37.94% (22/58)
IgG λ MM	17.24% (10/58)
IgA k MM	13.79% (8/58)
IgA λ MM	13.79% (8/58)
k LCMM	5.17% (3/58)
λ LCMM	12.07% (7/58)
rFLC (normal range: 0.26l -1.65)	213.31±555.65
% Abnormal	89.66%(52/58)
FLC I/U (request therapy >100)	368.34±668.75
% Abnormal	50% (29/58)
dFLC (I-U)	1729.24±2879.30
BJ (% presence)	70.69% (41/58)
Bone lesions (% presence)	82.76% (48/58)

HB = haemoglobin; PLT = platelets; MC = monoclonal component; BJ = Bence-Jones proteinuria;
I= involved chain; U= uninvolved chain; MM=Multiple Myeloma

TABLE 2. Values of dFLC, rFLC and their comparison in relation to renal function parameters in patients Group 1 and Group 2. Groups 1 and Group 2 were obtained considering dFLC and rFLC values in patients with abnormal and normal score respectively of BJ, Serum Creatinine, Albuminuria and Proteinuria parameter".

PARAMETER	GROUP 1 DFLC MEAN ± SD (NR.)	GROUP 2 DFLC MEAN ± SD (NR.)	GROUP 1 VS. GROUP 2 DFLC P-VALUE
BJ	2322.91±3275.89 (41)	297.47±377.69 (17)	0.0001* (MW)
Serum Creatinine	1636.18±2299.25 (35)	1870.85±3694.80 (23)	0.994 (MW)
Albuminuria	2650.61±3657.38 (31)	671.37±940.87 (27)	0.0016* (MW)
Proteinuria	2327.19±3393.21 (38)	593.14±901.09 (20)	0.0025* (MW)
Parameters	Group 1 rFLC mean ± SD (Nr.)	Group 2 rFLC mean ± SD (Nr.)	Group 1 vs. Group 2 rFLC p-value
BJ	283.84±650.65 (41)	43.22±131.72 (17)	0.84 (MW)
Serum Creatinine	157.77±444.02 (35)	297.83±704.91 (23)	0.93 (MW)
Albuminuria	320.77±730.96 (31)	89.93±206.52 (27)	0.60 (MW)
Proteinuria	274.11±667.31 (38)	97.80±232.11 (20)	0.63 (MW)

* = Significant test (p-value<0.05); MW = Mann − Whitney test; BJ = Bence-Jones proteinuria; Group 1: dFLC and rFLC in patients with abnormal value of renal parameters; Group 2: dFLC and rFLC in patients with abnormal value of renal parameters

we suggest a study with a larger study sample to reduce possible statistical biases. Anyway these limitations do not diminish the significance of our results.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Salvatrice Mancuso: conceived and designed the study and wrote the manuscript.
Melania Carlisi: contributed to the study design, enrolled the patients and wrote the manuscript.
Nicola Serra: statistical analysis, interpretation of data and wrote the manuscript.
Mariano Sardo: collected data.
Giuseppe Bertuglia: collected data.
Emanuela Pappalardo: performed laboratory tests.
Sergio Siragusa: critically revised the manuscript.
All authors have read and approved the manuscript.

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