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Review Article

Significance of Serum Free Light Chains in Prognosis and Monitoring of Multiple Myeloma: A Review

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ABSTRACT

Patients suffering from multiple myeloma show considerably variable outcomes in terms of prognosis. Survival may be as short as few months in refractory disease, while those with mild disease may live beyond a decade. Abnormally higher levels of serum free light chains and abnormal kappa to lambda ratios are found in the majority of cases. The severity of disease correlates with the elevation and abnormal ratio of these free light chains. These values and ratios are widely used to determine the prognosis and to monitor the disease activity and response to chemotherapy. They provide important clues to clinicians which might help them tailor the treatment protocols and make future therapeutic plans. The objective of this article is to review the importance of serum free light chains in the prediction of prognosis, monitoring of disease activity and evaluation of therapeutic response in multiple myeloma patients. We undertook a comprehensive systematic search of medical literature available on electronic databases. It is found that there is a linear relationship between disease activity and SFLC values as well as degree of abnormality of its ratios. Extremely high serum free light chains values indicate refractory disease while minimal elevation at baseline and normalization after chemotherapy is considered as a favorable sign. Similarly, highly abnormal ratios indicate poor outcomes while the effectiveness of chemotherapy was reflected by normalization of these ratios.

Keywords: Multiple myeloma; Serum free light chains; Prognosis; Monitoring

INTRODUCTION

Patients suffering from multiple myeloma exhibit highly variable outcomes [1]. There is a dramatic difference in the survival time which may range from few months to more than a decade depending upon the severity of the disease [2] Majority of patients suffering from multiple myeloma have elevated levels of kappa or lambda light chains in serum, or an abnormal ratio between these two chains is observed [3]. Immunoassay of these light chains has been a reputable diagnostic monitoring modality for light chain multiple myeloma [4]. Free light chains are probably more useful than other diagnostic tests and their short half-life makes them a dependable scale of therapeutic response [5] Baseline values of light chains provide a clue for the degree of aggressiveness and its normalization after treatment predict a satisfactory response [2] The aim of this article is to provide a comprehensive review of the prognostic importance of serum free light chains in multiple myeloma.

METHODS

Electronic databases namely Pubmed, Science Direct, Ovid and Wiley were searched for relevant articles. Articles from the inception of databases till February 2019 were included in the search. Keywords for our search included “Multiple Myeloma”, “Serum Free Light Chains” and “Prognosis”. All potential articles were identified and listed for removal of duplicate ones. After duplicate articles were removed, abstracts assessment was carried out. Relevant articles were selected for full-text assessment and a total of eighteen studies were included in the final review.

RESULTS

Free light chains and their ratios are of utmost importance for the determination of prognosis and monitoring of multiple myeloma. Baseline values at diagnosis, values after therapy and their normalization have a distinct implication. Extreme elevations of these values and highly abnormal ratios at baseline are associated with refractory and high-grade disease, on the other hand, minimal elevations and slight abnormalities in ratios are considered as

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a mild disease and some case can be monitored closely without any intervention. Comparison of baseline values and values after chemotherapy is a reliable way to evaluate the effectiveness of chemotherapy. Normalization of its values and ratios is considered as a marker of therapeutic success, conversely persistently elevated values and an abnormal ratio might indicate the suboptimal results of the chemotherapeutic regimen. For the sake of convenience, we have divided the findings into three groups.

Importance of baseline values

Myeloma patients with exceptionally high SFLC values (>1000 mg/dL) at diagnosis, it was observed that higher levels of SFLC predict an extremely grim prognosis in multiple myeloma. Fifteen patients were enrolled with SFLC levels of >1000 mg/dL. Median age and median survival for these participants were reported as 60.81 and 1.85 years sequentially. Nine patients received autologous PBSCT and six of them were reported to be alive at the time of publication with median survival of 2.44 years and mean survival of 3.8 years. Rest of six didn't get previously mentioned intervention, and 3 of those were reported to be alive with median and median survival of 1.21 and 1.20 years. It was ascertained that these patients exhibited highly unfavorable prognosis [2].

A review study published in 2014 emphasized the importance of baseline SFLC levels in the prediction of survival. It was stated that quantitative analysis of SFLC is mandatory for monitoring and evaluation of therapeutic response [6].

Serum free light chain values are superior to urine counterparts in terms of sensitivity. In a study comparing the utility of serum and urine free light chain analysis, it was reported that SFLC were found in sera of all patients, but only 64% of patients yielded a positive light chain (Bence Jones Protein) via urine protein electrophoresis. It was concluded that serum free light chain analysis has a higher sensitivity and it should be preferred over urine protein electrophoresis [7].

Although one study claimed that SFLC has no significant implication in the prognosis of Tate et al. [8] examined sera from thirty-four patients suffering from multiple myeloma and suggested that baseline measurements of SFLC might not be valuable in the prediction of reoccurrence.

The implication in the assessment of therapeutic response

Therapeutic responses can be assessed by reduction in serum free light chains in multiple myeloma. This has been proven by numerous studies. Mead et al. conducted a study in 2004 to ascertain the importance of serum free light chain values in repose to chemotherapy. This study included 493 British patients diagnosed with multiple myeloma. Samples of SFLC from seventeen patients were analyzed and compared with other biomarkers, a faster decline was observed in the values of SFLC as compared to intact immunoglobulin. Moreover, a greater degree of concordance was observed with beta 2 microglobulin levels and plasma cell volume. This study concluded that SFLC levels can be used in almost all patients for monitoring purpose in multiple myeloma [4].

Another study exemplifies the importance of SFLC values for grading of chemotherapeutic response. Hansen and coworkers undertook a study on 36 MM patients, intact SFLC concentrations were measured serially after the commencement of chemotherapy. Patients with beeline SFLC value of >75 mg/dL demonstrated a remarkable one fifth reduction. Mean decrease was reported to be 52.3 and 23.6 percent for very Good Partial Response (VGPR) and Partial Response (PR) respectively. Eight percent decline in SFLC value predicted VGPR with 87.5% sensitivity and 100% specificity. It was deducted that early deduction in SFLC values is expected to be helpful for the assessment of chemotherapeutic response [3]. Another study indicated that the SFLC concentration of >100 mg/L after therapy represented a poor overall and progression-free survival [5].

Jung et al. [9] studies 51 multiple myeloma patients for evaluation of practicality of SFLC. It was observed that patients attaining an adequate therapeutic response demonstrated normal or subnormal SFLC values. Hence, SFLC measurement was regarded as suitable monitoring modality for chemotherapy response due to shorty half-life of SFLC.

Watanaboonyongcharoen et al. [10] carried out a study comprised of 38 multiple myeloma patients in Thailand. Survival depended mostly on the response after the first cycle of chemotherapy. Those who attained more than fifty percent reduction in SFLC concentrations had 88% two-year survival, while 53.1% two-year survival was reported for those who demonstrated less reduction. It was concluded that the rapid decline in SFLC values after chemotherapy is a valuable marker for therapeutic response and overall survival in multiple myeloma patients.

Significance of kappa to lambda ratio

Serum free light chain ratio provides important information for the prediction of survival and progression of disease in multiple myeloma patients [11]. Normalization of SFLC concentration and kappa to lambda ratio is a powerful sign of favorable response. Iwama et al. [12] followed 126 multiple myeloma patients and obtained SFLC values to evaluate treatment efficacy. Thirty-four patients demonstrated complete response, 37 very good partial response, 39 partial response and 16 exhibited constant disease pattern at 28 months follow-up. Normalization of ratio was observed in fifty-two patients who showed superior progression-free survival and overall survival (3-year survival of 94%) in comparison with those who had an abnormal ratio (3-year survival of 48%). It was ascertained that normalization of kappa to lambda ratio is an independent marker of a favorable outcome.

In another study conducted by Kyrtsonis et al. [13] which highlighted the prognostic impact of serum free light chains ratio, ninety-four Greek patients were enrolled and their SFLC ratio was calculated. According to final results, three and five-year survival was 94% and 82% respectively, in the 'low' serum free light chains ratio group of participants in comparison with 58% and 30% in the 'high' serum free light chains ratio group. It was deduced that serum free light chains ratio is an independent marker of prognosis.

Larsen et al. [14] carried out a study in the United States in 2012 to investigate the importance of serum free light chains ratio in high risk smoldering multiple myeloma. It was proposed by this study that an abnormally high SFLC ratio indicates an imminent progression of the disease. A total of 586 patients' data was retrospectively studied and it was concluded that the risk of progression in patients with SFLC ratio of 100 or more was 72% in the first two years. It was recommended that patients with SFLC ratio of 100 or more were at high risk of progression and timely intervention was necessary for these patients.

Another study conducted in Malaysia signify the prognostic importance of baseline SFLC ratio at the time of diagnosis. A worse survival profile (30 months) was observed in patients with abnormal SFLC ratio (<0.04 and >57.5) in comparison with patients with SFLC ratio of >0.04 and <57.5 (48 months). It was concluded that baseline kappa to lambda ratio provides important prognostic information [1].

Naggar et al. [15] examined forty-five newly diagnosed multiple myeloma patients to assess the significance of SFLC ratio in terms of survival and measurement of therapeutic response. SFLC ratios at diagnosis and after therapy were compared. A dramatic difference in the SFLC ratio was observed who responded well to treatment. A poor survival profile was found in patients with SFLC ratio of >2.6 and <0.56 in comparison with patients having SFLC ratio spanning between 0.56 and 2.6.

Garcia et al. [16] followed 180 multiple myeloma patients for 35 months to examine the importance of SFLC. It was concluded that SFLC ratio has a substantial contribution for prediction of survival and an SFLC ratio of 47 or more has independent predictive importance at the time of diagnosis. In another study conducted by Tacchetti et al. [17] in Italy, 150 multiple myeloma patients were examined using serial measurements of SFLC. Patients were divided into three groups on the basis of SFLC ratio, group 1: normal, group 2: lightly abnormal (<100) and highly abnormal (>100), progression-free survival was calculated as 72%, 61%, and 41% respectively for groups 1-3. Furthermore, it was noted that patients who attained normalization of SFLC ratio showed longer overall and progression-free survival.

In a fairly recent study conducted by Lyubimova et al. [18] in Russia, prognostic competence of SFLC ratio was examined using data from 118 multiple myeloma patients.

DISCUSSION AND CONCLUSION

Taking all available evidence into consideration, it can be ascertained that the measurement of serum light free chains is particularly important for prognosis and monitoring of multiple myeloma patients. Its baseline values provide important clues for overall and progression-free survival. The decline in its values after chemotherapy is a marker of therapeutic response. Abnormal kappa to lambda ratios signify poor prognosis, while normalization of this ratio is considered a favorable sign after chemotherapy. Research on these utilities of serum free light chains is still its infancy. Further studies are needed to elucidate the exact role of serum free light chains in multiple myeloma. Studies should focus on validity and reproducibility of results and a reliable scale of serum free light chains and its ratios should be developed to guide the prognosis, monitoring, and estimation of therapeutic response in multiple myeloma patients.

Remarkable differences were observed in terms of overall and progression-free survival in two groups on the basis of SFLC ratio. It was reported that baseline κ/λ ratio of less than 0.04 and more than 140 represent a grim prognosis [18].

In contrast, a study was conducted recently by Lopez-Anglada et al. [5] in Spain to assess the predictive practicality of serum light chains ratio. A total of 819 patients were involved and serum samples collected at the time of diagnosis and samples after therapy were analyzed. It was concluded that an abnormally high SFLC ratio was not significantly related to progression. Moreover, it was proposed that normalization of SFLC ratio did not indicate a superior response among patients who attained complete response.

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CONFLICT OF INTEREST

The authors have no conflict of interests to disclose.

REFERENCES

1. Sthaneshwar P, Nadarajan V, Maniam JA, Nordin N, Gin Gin G. Serum free light chains: Diagnostic and prognostic value in multiple myeloma. Clin Chem Lab Med. 2009;47:1101-1107.
2. Chilkulwar A, Mewawalla P, Miller A, Berteotti G, Sahovic E, Lister J. Serum free light chain concentration (>1000 mg/dl) at diagnosis and at relapse predicts for very poor prognosis in multiple myeloma. Blood. 2016;128:5698.
3. Hansen CT, Pedersen PT, Nielsen LC, Abildgaard N. Evaluation of the serum free light chain (sFLC) analysis in prediction of response in symptomatic multiple myeloma patients: Rapid profound reduction in involved FLC predicts achievement of VGPR. Eur J Haematol. 2014;93:407-413.
4. Mead GP, Carr-Smith HD, Drayson MT, Morgan GJ, Child JA, et al. Serum free light chains for monitoring multiple myeloma.Br J Haematol. 2004;126:348-554.
5. Lopez-Anglada L, Cueto-Felgueroso C, Rosinol L, Oriol A, Teruel AI, de la Guia AL, et al. Prognostic utility of serum free light chain ratios and heavy-light chain ratios in multiple myeloma in three PETHEMA/GEM phase III clinical trials. PLoS One 2018;13:e0203392.
6. Graziani MS, Merlini G. Serum free light chain analysis in the diagnosis and management of multiple myeloma and related conditions. Expert Rev Mol Diagn. 2016;14:55-66.
7. Dejoie T, Corre J, Caillon H, Hulin C, Perrot A, Caillot D, et al. Serum free light chains, not urine specimens, should be used to evaluate response in light-chain multiple myeloma. Blood. 2016;128:2941-2948.
8. Tate J, Mollee P, Gill D. Serum free light chains for monitoring multiple myeloma. Br J Haematol. 2005;128:405-406.
9. Jung S, Kim M, Lim J, Kim Y, Han K, Min CK, et al.Serum free light chains for diagnosis and follow-up of multiple myeloma.Korean J Lab Med. 2008;169-173.
10. Watanaboonyongcharoen P, Suwannabutra S, Theerasaksilp S, Paripokee N, Di Nakorn T. A420 the roles of serum free light chain assay on the prognosis of multiple myeloma. Clin Lymphoma Myeloma Leuk. 2009;9:S66.
11. Tosi P, Tomassetti S, Merli A, Polli V. Serum free light-chain assay for the detection and monitoring of multiple myeloma and related conditions. Ther Adv Hematol. 2013;4:37-41.
12. Iwama K, Chihara D, Tsuda K, Ugai T, Sugihara H, Nishida Y, et al. Normalization of free light chain kappa/lambda ratio is a robust prognostic indicator of favorable outcome in patients with multiple myeloma. Eur J Haematol. 2013;90:134-141.
13. Kyrtsonis MC, Vassilakopoulos TP, Kafasi N, Sachanas S, Tzenou T, Papadogiannis A, et al. Prognostic value of serum free light chain ratio at diagnosis in multiple myeloma. Br J Haematol. 2007;137:240-243.

14. Larsen JT, Kumar SK, Dispenzieri A, Kyle RA, Katzmann JA, Rajkumar SV. Serum free light chain ratio as a biomarker for high-risk smoldering multiple myeloma. Leukemia. 2013;27:941-946.

15. El Naggar AA, El-Naggar M, Mokhamer el H, Avad MW. Prognostic value of serum free light chain in multiple myeloma. Egypt J Immunol. 2015;22:69-78.

16. García de Veas Silva JL, Bermudo Guitarte C, Menéndez Valladares P, Rojas Noboa JC, Kestler K, Duro Millán R. Prognostic Value of Serum Free Light Chains Measurements in Multiple Myeloma Patients. PLoS One. 2016;11:e0166841.

17. Tacchetti P, Cavo M, Rocchi S, Pezzi A, Pantani L, Brioli A, et al. Prognostic impact of serial measurements of serum-free light chain assay throughout the course of newly diagnosed multiple myeloma treated with bortezomib-based regimens. Leuk Lymphoma. 2016;57:2058-2064.

18. Lyubimova NV, Timofeev YuS, Votyakova OM, Kushlinskii NE. Free light chains of immunoglobulins in the diagnosis and prognosis of multiple myeloma. Alman Clin Med. 2018;45:102-108.