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CLINICAL RESEARCH

Monoclonal Light Chains in Multiple Myeloma: The Sinister Immunoglobulin

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Abstract

Multiple myelomas are the commonest hematological malignancy in adults, next to the heterogeneous group non-Hodgkin lymphomas, and account for about 10% of such tumors. About 21% of the multiple myelomas are associated with higher levels of free monoclonal light chains. This subgroup of patients exhibits high incidence of renal disease manifested by significantly lower estimated glomerular filtration rate, higher incidence of dialysis and significantly shorter survival.

We have defined criteria for identification of high risk patients with light chain only as well as intact immunoglobulin myelomas. Kappa and lambda light chain specific criteria have been enunciated for intact immunoglobulin multiple myelomas and the need for development of similar criteria for light chain only myelomas has been identified.

The strengths and weakness of the assays for measuring serum free light chains are addressed, in general and the irregularities introduced by the use of kappa/lambda ratio are highlighted. We address the state of the art for detection of monoclonal free light chains in serum. The low rate of utilization of urine for identification of monoclonal light chains is emphasized, given the historical importance of the assay as well as the specificity of the test in unequivocal detection of monoclonal light chains by immunofixation electrophoresis.

The need for treatments addressing the specific needs of patients with high light chain associated lesions is highlighted. The current approaches of plasmapheresis and large bore hemodialysis have not shown consistent beneficial results and specific chemotherapies need to be evaluated in prospective trials.

Keywords

Multiple myeloma, Monoclonal light chains, FLC-Modified SIFE, MASS-FIX/MALDI, Light chain predominant multiple myeloma, Cast nephropathy

Précis

immunoglobulins secreted by plasma cells, the maturation endpoint of the B lymphocyte lineage, are the primary molecules mediating humoral immunity. Plasma cells generally produce more light chains than heavy chains. Excess free light chains can be detected in normal serum and urine. Based on the principle of allelic exclusion, lymphocytes rearrange the kappa chain loci first and engage lambda chain loci only if the rearrangement for kappa chain DNA is unsuccessful. Due to this hierarchical rearrangement process, there is natural predominance of kappa-restricted light chains over lambda-restricted light chains and kappa associated intact immunoglobulins over lambda associated ones. While the same regulatory framework underlies immunoglobulin gene rearrangement in neoplastic plasma cells, the immunoglobulin expression profiles may be markedly altered. Malignant transformation of plasma cells results in a common hematological malignancy termed multiple (plasma cell) myeloma.

Monoclonal light chains were the first tumor marker used to diagnose and monitor malignancy, namely the Bence Jones proteins in urine of patients with multiple myeloma. Monoclonal light chains in serum and urine

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continue to provide a robust marker for neoplastic disorders of plasma cells.

Measurement of serum free light chains (SFLC) is in widespread use as an adjunct in the diagnosis and monitoring of monoclonal gammopathies. However, the assay has not undergone harmonization and alternative methods in current laboratory practice do not provide equivalent results. In order to normalize effects of immunoglobulin production, the use of a SFLC kappa/lambda ratio has been recommended for common use. However, the generally accepted reference ranges have a high number of false positives and false negatives and may provide misleading results especially in patients status post hematopoietic stem cell transplantation.

Although monoclonal immunoglobulin light chains in urine was the index tumor marker in the previous century, examination of urine is an underutilized test for detection of monoclonal light chains. Urine examination can rectify the erroneous implications of abnormal kappa/lambda ratios. Detection of monoclonal light chains in urine is pathognomonic of monoclonality, whereas an abnormal kappa/lambda ratio is not. Urine examination by immunofixation electrophoresis should garner wider use to obviate problems with diagnosing monoclonal gammopathy, especially to diagnose and monitor light chain only neoplastic disorders.

In about 15% of patients, plasma cells in multiple myeloma secrete light chains only without an associated heavy chain moiety; this is termed light chain multiple myeloma (LCMM). Among patients with LCMM, a subgroup of 40% of patients produce significantly higher amounts of neoplastic free monoclonal light chains, and this subgroup is associated with significantly worse overall prognosis, with patients developing lower eGFR and significantly shorter survival.

In multiple myeloma lesions producing intact immunoglobulins, a subgroup of about 18% produce a significant excess of neoplastic free monoclonal light chains; these are termed light chain predominant multiple myelomas (LCPMM). This subgroup is associated with significantly higher renal damage as expressed in lower eGFR, and higher rates of dialysis. Patients with LCPMM have a shorter survival by about 2 years compared to patients with stoichiometrically nearly equal heavy and light chain constituents.

Serum levels of involved neoplastic light chains serve as a useful tumor marker in LCMM and LCPMM. A newly developed assay, FLC-Modified serum immunofixation electrophoresis (FLC-Modified SIFE), for monoclonal free light chains in serum promises to provide a sensitive marker for monitoring the course of disease, including detection of minimal residual disease. The assay has shown greater sensitivity than the current state-of-the-art diagnostic tests.

Given the poorer survival in LCMM with high concentration of neoplastic light chains, and LCPMM, patients constituting this group should be identified in prospective trials. Specific efforts to rapidly reduce the serum levels of neoplastic free light chains may be important in preventing irreversible renal damage and attendant shorter survival.

Multiple myeloma and other light chain disorders are also associated with pathogenesis of AL amyloid. There is wide variation in light chain pathology in AL amyloid and monitoring concentration of light chains has not been standardized for diagnosis or monitoring of AL amyloid. Amyloidosis is a refractory plasma cell disorder with widespread systemic effects and limited therapeutic interventions.

Background

Immunoglobulins are an integral part of the adaptive host defense system. Immunoglobulins, as functional antibodies, are the primary response to microorganism and parasitic infections. Immunoglobulins consist of heavy and light chains. The heavy chains are designated gamma, for IgG, alpha for IgA, mu for IgM, delta for IgD and epsilon for IgE. The light chains are kappa and lambda. IgG, IgD and IgE usually consist of two heavy and two light chains, IgA in serum usually has two heavy and two light chains, however, the IgA in secretions is dimeric with four heavy and four light chains plus a J piece and a secretary piece. IgM is pentameric, consisting of 10 heavy chains and 10 light chains. In normal immune physiology, each immunoglobulin molecule incorporates only one type of heavy and one type of light chain [1,2].

Both the heavy and light chains contain constant and variable regions. The variable regions impart antigen specificity. The diversity of immunoglobulins is accomplished primarily by rearrangement of DNA for the variable regions of heavy and light chains, supplemented by somatic mutation. The combination of DNA rearrangement and somatic hyper mutation during the maturation process of immunoglobulin development can theoretically generate more than 10^{16} unique types of immunoglobulins molecules each with specificity for different antigens/epitopes [3-5].

Greater abundance of kappa than lambda light chains

During the process of DNA rearrangement, the lymphocyte usually rearranges the DNA for kappa light chain first, and if neither allele can be rearranged successfully, the cell rearranges the DNA for lambda light chain; this biologic paradigm is termed allelic exclusion. This biological preference/priority for kappa light chains accounts for dominance of kappa light chain associated immunoglobulins over lambda light chain associated immunoglobulins. The ratio of kappa to lambda is about 2:1 in humans. In mice the ratio is 19:1 explaining the observation that virtually all mouse derived monoclonal

antibodies are IgG kappa. The preference for kappa over lambda light chains is accentuated in immune responses to infections and other inflammatory conditions [4-10].

Plasma cells, the mature form of immunoglobulin secreting lymphocytes, usually produce more light chains than heavy chains and the excess free light chains can be detected in serum. Light chains are small molecules with a mass of about 25kDa, and excess free light chain proteins are filtered through the glomerulus. The filtered light chains are absorbed by renal tubular cells and the amino acids of degraded light chains are reutilized. A small amount of free light chain proteins is detectable in urine in the normal healthy human state [11,12]. Neoplastic plasma cells secrete variable amounts of excess free light chains. At one extreme are lesions in which only light chains are produced and secreted, e.g., light chain multiple myelomas; at the other extreme is lack of detectable excess of free light chains as is sometimes seen in lambda light chain associated multiple myelomas [8,10,13-15].

Excess free monoclonal light chains are also present in the serum and urine in other disorders of plasma cells and lymphoplasmacytic tumors. The premalignant disorders of monoclonal gammaopathy of undetermined significance (MGUS) and smoldering/asymptomatic multiple myeloma (SMM) usually produce excess free monoclonal light chains and may produce only monoclonal light chains. Waldenstrom macroglobulinemia, and other B-cell lymphomas also produce excess free light chains in addition to intact immunoglobulins. AL amyloidosis and light chain deposition disorders are associated with variable excess monoclonal light chains detectable in serum and urine [10,16,17].

Serum free light chains (SFLC)

Quantification of immunoglobulins is usually performed by nephelometric assays using antibodies to class and sub-class specific antisera directed to heavy chains. Antibodies to heavy and light chains are in common use in serum immunofixation electrophoresis (SIFE) to identify the monoclonal immunoglobulins. The commonly available antisera to light chains react with light chains bound to intact immunoglobulin as well as free light chains. In a paradigm-shifting development, Bradwell generated antisera to only the epitopes of light chains that are hidden in intact immunoglobulins, i.e., the antisera are specific for free light chains. Commercial reagents to quantify serum free light chains have been available since about 2001 [18].

Commercial antisera to SFLC were employed by Mayo Clinic investigators to establish reference ranges for kappa and lambda SFLCs. A distorted kappa/lambda ratio has been promoted in the oncology literature as a diagnostic tool to identify neoplastic disorders of plasma cells [19-21]. However, invoking the kappa/lambda ratio as a solitary assay generates excessive false negative and false positive results; accordingly, the original investigators did not propose it as a diagnostic test [9,10,14,19-24]. The investigators suggested using SPEP and SFLCA as a screening test for monoclonal immunoglobulins would detect virtually all cases of multiple myeloma [21]. The International Myeloma Working Group (IMWG) proposed a normal kappa/lambda ratio as one of the requirements for stringent complete response; however, use of this parameter has also been challenged due to a large number of discordant results in monitoring disease progression, especially in patients status-post hematopoietic stem cell transplantation [10,22-25].

Another shortcoming of the SFLC assay is the lack of harmonization of the assays. Using reagents from a given source, different instruments/platforms do not generate equivalent values. If SFLC concentration is used to monitor the course of illness, as is pertinent in patients with light chain multiple myeloma, it would be prudent to use the same method and preferably the same laboratory, as is the usual recommendation for other tumor markers as well [15,26-30].

Identification and measurement of monoclonal serum free light chains

A significant shortcoming of the assays for SFLCs and kappa/lambda ratio is the inability of such assays to distinguish between polyclonal and monoclonal free light chains. In extreme cases, a serum concentration of a free light chain of >100mg/L has been noted in patients with a reactive polyclonal increase and lack of a monoclonal neoplastic process [10,31,32]. Monoclonal free light chains are detectable on SIFE in patients with light chain multiple myelomas and amyloid when such light chains are present in sufficient concentration. Even in patients with intact immunoglobulin multiple myeloma, excess free monoclonal light chains may be detectable on SIFE if the free light chains are present in sufficient concentration and migrate in a different location than the intact immunoglobulin monoclonal protein. Dimeric or multimeric light chains, usually with lambda restriction, are easier to detect on SIFE [10,32,33].

A number of methods have been proposed to detect free monoclonal light chains in serum, namely, Quantitative Ultra filtration Immunofixation Electrophoresis Test (QUIET), FLC-Modified SIFE using antisera specific to free light chains, and Nanobody Enrichment Coupled to MALDI-TOF mass spectrometry (MASS-FIX/MALDI). MASS-FIX/MALDI has been presented as a method to replace conventional SIFE and as a tool for detecting minimal residual disease [34,35]. However, parallel testing with the newly described Free Light Chain Modified SIFE (FLC- Modified SIFE) demonstrated a high rate of failure in detecting

monoclonal light chains by MASS-FIX/MALDI. In addition MASS-FIX/MALDI reported a number of false positive findings of monoclonal light chains as well as intact monoclonal immunoglobulins, casting doubt on the validity of this technique to replace SIFE let alone use as a test for minimal residual disease [31,32,34-41].

Light chain predominant multiple myelomas and greater abundance of kappa light chains

About 15% of multiple myeloma lesions produce only light chains, i.e., light chain multiple myeloma (LCMM) [10,42]. The concentration of monoclonal free light chains varies among different patients, as is the case with monoclonal immunoglobulin in conventional intact immunoglobulin multiple myelomas. In about 18% of the intact immunoglobulin producing multiple myelomas, there is a marked excess of free monoclonal light chains, i.e., light chain predominant multiple myeloma (LCPMM) [43,44]. Higher levels of monoclonal light chains in multiple myeloma patients have been known to be associated with higher incidence of renal disease. A threshold for identification of higher concentrations of monoclonal SFLC has been controversial in the literature and levels of 47, 500, 700 and 800 mg/L have been proposed [45-49]. These studies did not elucidate light chain type specific criteria even when a fivefold greater median level for kappa vs. lambda light chain levels was documented [45]. It has also been demonstrated that per gram of monoclonal immunoglobulin, neoplastic plasma cells produce four times more kappa light chains than lambda light chain [8]. The pathogenic role of free monoclonal light chains, especially for kidney disease is well documented [42-48].

Toxicity of monoclonal free light chains:

Identification and quantification of monoclonal free light chains has gained prominence with the recognition of the exquisite toxicity of monoclonal light chains. It is worth noting that the physical identification of monoclonal light chains in urine constitutes the first known instance of a tumor marker in the form of Bence Jones protein. The presence of monoclonal light chains in urine is now generally referred to as Bence Jones proteinuria, though not all monoclonal light chains exhibit the temperature dependent precipitation characteristics of “Bence Jones” protein, originally described by Dalrymple, Bence Jones and MacIntyre [49]. (Three original publications, based on the findings from a single patient, by Dalrymple, Bence Jones and MacIntyre were not reviewed and are cited from the publication by Steven I Hajdu, reference number 49). Nevertheless, examination of urine for monoclonal light chains by urine immunofixation electrophoresis (UIFE) is an important laboratory test. The recommendations for using a serum free light chain quantitative assay (SFLCA) to replace urine testing notwithstanding, it is important to stress that an altered SFLC ratio is not diagnostic of monoclonaltiy, whereas detection of monoclonal light chains in urine is pathognomonic for a monoclonal lesion [10,32,42,50-54]. All light chain multiple myelomas have been documented to have monoclonal light chains in urine at the time of diagnosis [52].

The dominant pathologic lesions associated with monoclonal light chains are renal damage, amyloidosis and perhaps systemic vascular lesions. In addition to their association with multiple myeloma, monoclonal light chains are also pathogenic in light chain deposition disease and amyloidosis [55-57]. Amyloidosis is more often associated with lambda light chain lesions and light chain deposition is more often associated with kappa monoclonal immunoglobulins [58]. Light chain associated amyloidosis, AL Amyloid, may be systemic or localized and has a multitude of clinical presentations [16,59-60]. Variations in carbohydrate content of light chains has been proposed as a pathogenic and diagnostic marker for monoclonal light chains in amyloidosis [16,60,61]. Since multiple myeloma is the primary disease addressed here, AL amyloid and monoclonal light chain deposition disease are not addressed further in this communication.

Based on the current paradigm, the renal damage from high levels of monoclonal light chains is mediated mostly through cast chain nephropathy [12,55]. The pathogenic light chains filtered through the glomerulus bind mainly to tubular protein, uromodulin (Previously termed Tamm Horsfall protein) and precipitate in renal tubules. This process ruptures renal tubules and induces interstitial inflammation. Additional mechanisms of renal damage include monoclonal light chain deposition disease, immunotactoid glomerulopathy, proliferative glomerulonephritis, light chain proximal tubulopathy, crystal storing histicytosis, crystalglobulinuria, inflammatory and profibrotic kidney injury, Fanconi syndrome, amyloidosis and vasculitis [55-58]. The systemic significance of monoclonal light chain-induced vasculitis and thrombotic microangiopathy warrants additional investigation, as generalized vasculitis has the potential to damage other vital organs as well [16,55,64]. Uncommon disorders include light chain renal stones, light chain crystal deposition in cornea, skeletal myopathy, pulmonary embolism, acquired cutis laxa, cutaneous light chain deposition disease, cholestasic hepatitis and light chain deposition liver disease [65-70].

Given the risk of irreversible renal damage by high levels of monoclonal light chains, it would be helpful to have specific criteria for identifying at-risk patients and to establish light chain specific diagnostic criteria. In patients with intact immunoglobulin monoclonal gammopathic lesions in general, and multiple myeloma in particular, it has been noted that kappa light chain associated lesions have four fold higher concentrations of involved (neoplastic) SFLCs [8,10,45].

Based on this observation, along with the finding that lambda light chain-associated intact immunoglobulin multiple myelomas have lower levels of monoclonal immunoglobulins, a metric of serum free light chains concentration in mg/L per gram of monoclonal immunoglobulin/dL has been proposed. In a retrospective study that identified and described diagnostic criteria for LCPMM, it was observed that the metric of SFLC in mg/L per g of monoclonal immunoglobulin/dL adequately identified LCPMM patients [43,44]. The three additional metrics, namely, SFLC concentration, involved to uninvolved SFLC concentration ratio, and involved to uninvolved concentration ratio divided by monoclonal immunoglobulin in g/dL did not materially affect the discriminative power of SFLC/g of monoclonal immunoglobulin. Analysis of change point threshold in the distribution of SFLC/g of monoclonal immunoglobulin for kappa and lambda light chain associated LCPMM revealed distinct change/inflection points for kappa and lambda light chain associated lesions. The values for kappa and lambda chain associated lesions were 67 mg/L per g of monoclonal immunoglobulin and 43.5mg/L per g of monoclonal immunoglobulin respectively. Patients with LCPMM, identified by using these thresholds, were observed to have a shorter survival by 22.5 months. The other major finding associated with LCPMM lesions was the significantly lower eGFR and significantly higher rates of patients dependent on dialysis. From these associations and the information in the literature, it was imputed that LCPMM patients suffered greater renal injury due to higher levels of monoclonal SFLCs resulting in significantly shorter survival [43,44]. A Kaplan Meier plot depicting the shorter survival in LCPMM patients is shown in the (Figure 1). The shaded areas represent 95% confidence interval. The survival in LCPMM was significantly shorter ($P < 0.001$, from log-rank test) [43,44].

In light of the significant pathology of excess free neoplastic light chains in MM patients, accurate measurement of monoclonal immunoglobulin and pathogenic light chains is important in identification of LCPMM patients. Serum levels of monoclonal immunoglobulins are usually measured by densitometric scanning of serum protein electrophoresis (SPEP) [10]. This estimation is generally appropriate in monoclonal immunoglobulins migrating in the gamma region, where limited interfering serum proteins co-migrate. However, for monoclonal immunoglobulins migrating in the beta region, estimation by densitometry is complicated by

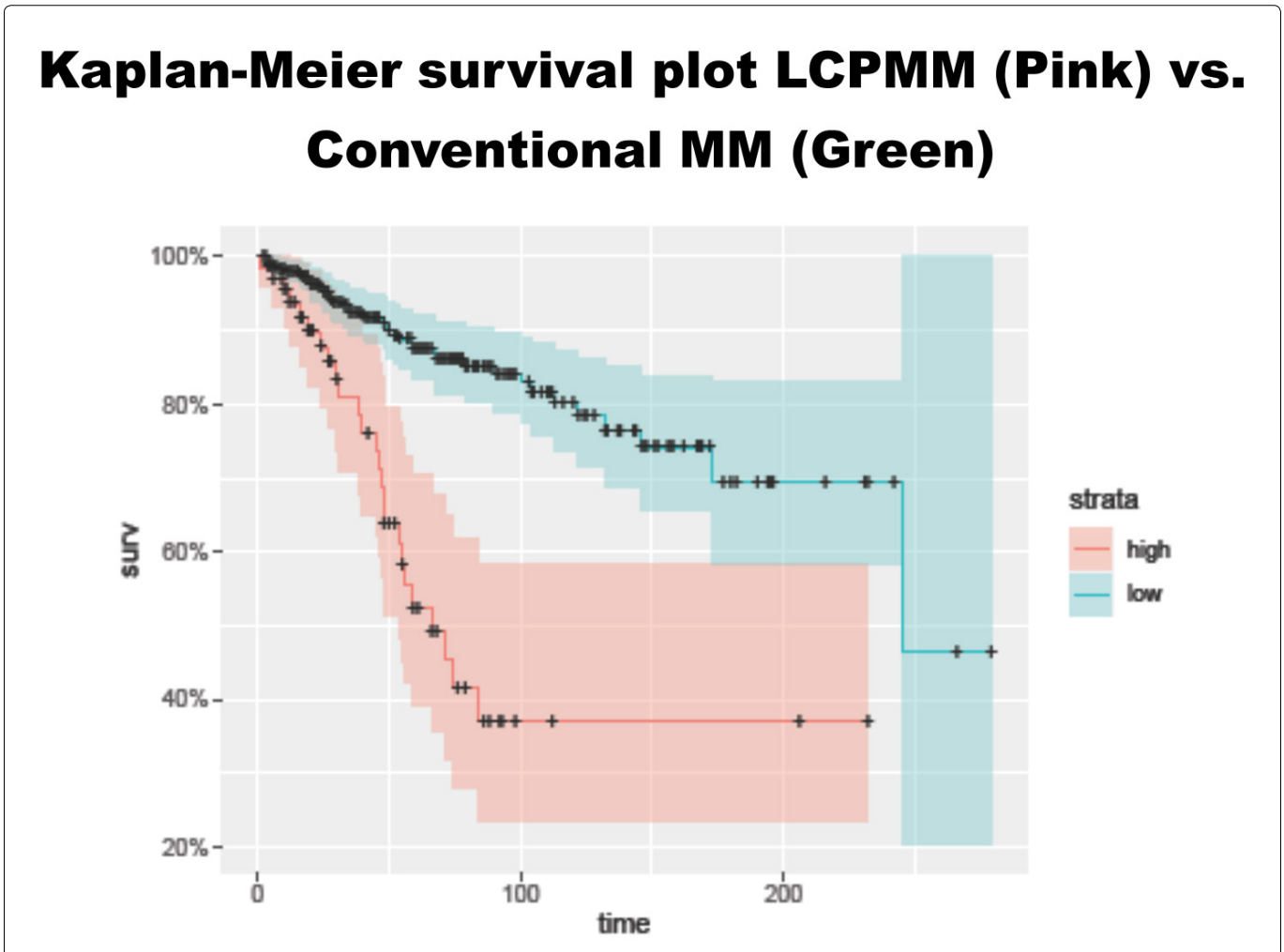

Figure 1: Survival curves for LCPMM patients (Pink) and patients with conventional MM (Green) are presented. The shaded areas represent 95% confidence interval. Survival in LCPMM patients is shorter, on average, by 22.5 months.

the interferences of proteins normally migrating in the beta region, namely, transferrin and C3 component of complement. In usual SPEP/SIFE results the combined concentration of monoclonal immunoglobulin and beta protein(s) is reported and is generally adequate for monitoring the course of illness. To ensure a more precise measurement of beta-migrating monoclonal immunoglobulins, a process has been described that abrogates the C3 band by heat treatment and adjusts for transferrin concentration by immunochemical measurement of this protein in serum. This method does not require capillary electrophoresis and provides comparably accurate estimates of beta-migrating monoclonal immunoglobulins. This modification to the usual densitometry quantification of monoclonal immunoglobulins allows a more precise measurement of monoclonal gammopathic proteins, thus facilitating more accurate identification and monitoring of LCPMM patients with beta migrating monoclonal immunoglobulin [71].

A similar change point analysis was performed for light chain immunoglobulins concentration in LCMM, however, the smaller number of observations from a single institution, did not allow development of a statistically relevant light chain specific change/inflection points. For the combined kappa and lambda LCMM a change point of 455 mg/L of SFLCs separated the patients with greater renal damage and significantly shorter survival. This group of patients with >455 mg/L of monoclonal light chains constituted 40% of the LCMM patients; this represents a greater fraction than light-chain predominant multiple myeloma as a fraction of intact immunoglobulin conventional MM patients. Clearly, a larger number of observations is needed to establish light chain-specific criteria for identifying LCMM patients at higher risk of renal damage and shorter survival [42]. In this regard, it is worth noting that light chain monoclonal gammopathy of undetermined significance is a relatively benign disorder and has a high spontaneous resolution rate [72].

As noted above, 40% of LCMM patients met the criterion for high concentration monoclonal light chain lesions. LCPMM constitute about 18% of the intact immunoglobulin multiple myelomas. Together the two high risk groups constitute about 21% of the total multiple myeloma population. [(0.15*0.4) + (0.85*0.18) = 0.213].

Effects of treatment for multiple myeloma on serum free light chain prevalence

Prior to initiation of treatment of patients with multiple myeloma, the SFLC concentration in LCMM and LCPMM can reasonably be expected to reflect the concentration of monoclonal light chains. However, following chemotherapy, and particularly following treatment with hematopoietic stem cell transplantation, (SCT) the frequent distortion of plasma cell populations often results in a transient oligoclonal pattern that interferes with determination of both intact monoclonal immunoglobulins as well as monoclonal SFLCs. About 70% of patients treated with SCT develop an oligoclonal pattern that has been shown to interfere with SFLCA results [10,22,73]. Thus, accurate determination of the presence of monoclonal light chains is important in monitoring these patients. Conventional SPEP and SIFE are usually not adequate in assessing the presence of monoclonal light chains. A more sensitive assay termed QUIET has been shown to identify monoclonal light chains and provide an estimate of the concentration of the monoclonal component by densitometry [31]. More recently, a method of FLC-Modified SIFE using antisera to free light chains has shown greater promise in accurate identification of monoclonal light chains in serum [32]. In a limited comparison with MASS-FIX/MALDI, the FLC-Modified SIFE demonstrated greater sensitivity in detecting monoclonal light chains in serum [32]. As and when curative treatment for multiple myeloma is developed, the FLC-Modified SIFE may also be useful in monitoring for minimal residual disease [32]. It is worth reiterating that the decline in urine testing may be depriving the laboratories of an easy method for initial diagnosis of monoclonal light chain lesions as originally advocated by Bence Jones and colleagues over a century and a half ago [10,49,50].

Need for treatments to address light chain toxicity

Despite the well-recognized toxicity of monoclonal light chains, no specific effective treatments for rapidly lowering the serum concentration of monoclonal light chains are available. While effective chemotherapy reduces the monoclonal light chain burden along with reduction in tumor mass, the treatment is not specifically targeted at the toxicity of monoclonal light chains [74,75]. Intravenous fluid therapy and dialysis with larger pore membranes have shown some salutary effect. Combinations of these treatment have shown beneficial effects in some trials. American Society for Aphaeresis gives therapeutic plasma exchange for myeloma cast nephropathy a grade 2B/Category II recommendation [76].

Rapid reduction in free monoclonal light chain burden is especially important in that aggressive early treatment has the potential to prevent permanent renal impairment. Two logical treatment approaches include plasmapheresis and dialysis with higher pore size membrane, but these modalities have not borne consistent beneficial results [12]. Intensive chemotherapy to prevent renal damage has not been systematically investigated in large controlled trials [77-79].

In summary; higher levels of monoclonal light chains in about 21% of multiple myeloma patients, are toxic to the kidney, and induce renal failure resulting in shorter survival. The criteria proposed for identification of

high concentration multiple myelomas could be used in prospective trials of treatments designed to rapidly reduce the serum levels of this sinister immunoglobulin.

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