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CITINGS

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The International Myeloma Foundation (IMF) *presents this special edition of CITINGS, our premiere publication featuring the most up-to-date information on multiple myeloma (MM) treatment and supportive care. This edition focuses on the Freelite® test, an established immunoassay panel that analyses free light chains, as well as the Hevylite® test, a novel immunoassay panel that analyses heavy chain/light chain pairs.*

It is our hope that CITINGS will help keep you abreast of the latest developments in myeloma treatment. As always, we welcome your feedback; you may contact the IMF at 800-452-CURE (2873) or at our website myeloma.org.

– Susie Novis, President, IMF

ASH PRESENTATIONS

SATURDAY, DECEMBER 10th

Evaluating Trends in Diagnostic and Prognostic Testing for Multiple Myeloma

C. J. Fidler, Ahmed Kamel Abou Hussein, Neel Gandhi, Vinit Karur, Manish Sharma, Thomas R Klumpp, Patricia Kropf, Mary Ellen Martin, Robert V. Emmons, and Kenneth F. Mangan.

Oral and Poster Abstracts: Health Services and Outcomes Research: Poster I

Time: 5:30 PM-7:30 PM **Location: Hall GH**
Abstract No.: 2067 **Session: 901**

The authors review the records of all patients with a diagnosis of MM referred to their center for autologous stem cell transplant between 2006 and 2011. They find that the most commonly omitted studies were the serum free light chains (SFLC), 24-hour urine and MM FISH panel. When assessed over time, compliance increased with the ordering of the SFLC assay, was stable for the MM FISH panel, and decreased for the 24-hour urine for Bence-Jones protein. This trend reflects the perception that the SFLC assay is replacing the 24-hour urine for Bence-Jones proteinuria.

Introduction: A battery of diagnostic and prognostic testing is recommended by both the NCCN and the International Myeloma Working Group (IMWG) at the time of diagnosis of myeloma (MM). It has been our observation that many patients referred for autologous stem cell transplant (ASCT) to our center have not had a complete MM workup. In this report, we attempt to quantify the adherence to recommended guidelines for the workup of MM. Methods: We reviewed the records of all patients with a diagnosis of MM referred to our center for ASCT between 2006 and 2011. We looked for the following tests at the time of diagnosis: bone marrow biopsy, SPEP, 24-hour urine for Bence-Jones proteinuria, serum β2 microglobulin, skeletal survey, serum free light chains, serum albumin, and MM FISH panel. We used descriptive statistics to evaluate our results. Results: There were a total of 64 patients who underwent an ASCT in our center between 2006 and 2011. Of these 64 patients, 9 patients were excluded from this review due to incomplete records. At the time of initial diagnosis, the most commonly obtained tests included an albumin level (55/55, 100%), SPEP (54/55, 98%), bone marrow biopsy (52/55, 95%), skeletal survey (52/55, 95%), standard cytogenetics (47/55, 85%), and β2-microglobulin (46/55, 84%). The most commonly omitted studies included the MM FISH panel (26/55, 47%), 24-hour urine for Bence-Jones protein (30/55, 55%), and serum free light chains (37/55, 67%). Compliance with the use of serum free light chain assay

Funded by an unrestricted educational grant from Binding Site.

improved over time, while the frequency of obtaining a MM FISH panel remains relatively low and the frequency of obtaining a 24-hour urine for Bence-Jones protein decreased. Conclusions: The most commonly omitted studies were the serum free light chains, 24-hour urine, and MM FISH panel. When assessed over time, compliance increased with the ordering of the SFLC assay, was stable for the MM FISH panel, but decreased for the 24-hour urine for Bence-Jones protein. This trend reflects the perception that the serum free light chain assay is replacing the 24-hour urine for Bence-Jones proteinuria. Referring community physicians need further education on the ordering of initial diagnostic and prognostic tests for MM.

Immunoglobulin Free Light Chain Levels Predict Survival in Primary Myelofibrosis and *de novo* Myelodysplastic Syndromes

Animesh Pardanani, Terra L. Lasbo, Christy Finke, S. Vincent Rajkumar, Preet Paul Singh, Rhett P. Ketterling, Curtis A. Hanson, Jerry A. Katzmann, and Ayalew Tefferi.

Oral and Poster Abstracts: Myeloproliferative Syndromes: Poster I

Time: 5:30 PM-7:30 PM **Location: Hall GH**
Abstract No.: 1756 **Session: 634**

The authors study two independent cohorts of patients with primary myelofibrosis (PMF) or myelodysplastic syndromes (MDS). They find that elevated plasma free light chain concentration predicts inferior survival in both PMF and MDS; its lack of correlation with leukemia-free survival and tumor-specific genetic markers suggests a primarily host-driven biological phenomenon that might be applicable to other malignant and non-malignant conditions.

Background: We hypothesized that surrogate markers of host immune response to clonal myeloproliferation predict survival in myeloid malignancies. Because of immediate applicability to current practice, we chose plasma immunoglobulin free light chain (FLC) concentration (B-cell activation marker) as the biomarker of interest. Patients and Methods: Two independent cohorts of patients with primary myelofibrosis (PMF) or myelodysplastic syndromes (MDS) were studied. Both groups were fully annotated for karyotype. Kappa (κ) and lambda (λ) FLC were measured by a quantitative nephelometric assay. Patients with monoclonal FLC were excluded. Results: Above upper normal-limit values for κ or λ FLC was documented in 33% of 240 study patients with PMF and 46% of 74 patients with MDS. Multivariable analysis revealed significant associations between increased FLC and elevated creatinine, as well as advanced age in PMF ($p=0.0004$) and hemoglobin <10 g/dL in MDS ($p=0.005$). Increased FLC predicted shortened survival in both PMF and MDS, independent of age, creatinine, and other conventional risk factors. Receiver-operating characteristic analysis-based cutoff levels for κ plus λ total FLC delineated risk groups with highly significant differences in overall survival; International Prognostic Scoring System-adjusted HR (95% CI) in PMF was 1.9 (1.3-2.7) and in MDS 6.3 (2.7-16.6). No correlations were seen with leukemia-free survival, karyotype or JAK2, MPL or IDH mutations. Conclusions: Elevated plasma FLC concentration predicts inferior survival in both PMF and MDS. Its lack of correlation with leukemia-free survival and tumor-specific genetic markers suggests a primarily host-driven biological phenomenon that might be applicable to other malignant and non-malignant conditions.

SUNDAY, DECEMBER 11th

Hevylite®, a Novel M-Component Based Biomarkers of Response to Therapy and Survival in Waldenström's Macroglobulinemia

Salomon Manier, Julie Lejeune, Lucile Musset, Eileen Boyle, Remy Dulery, Houria Debarri, Jean-Luc Faucompret, Jordan Gauthier, Claire Bories, Guillemette Fouquet, Charles Herbaux, Sabine Tricot, Annie Pietrantuono, Frederic Combat, Stephanie Poulain, Stephen Harding, Véronique Leblond, and Xavier Leleu.

Oral and Poster Abstracts. Non-Hodgkin Lymphoma - Biology, excluding Therapy: Poster II

Time: 6:00 PM-8:00 PM **Location: Hall GH**
Abstract No.: 2667 **Session: 622**

The authors seek to determine whether Hevylite® value can be used as a reliable marker for response to therapy in Waldenström's Macroglobulinemia (WM) as compared to the M-spike measurement. They also seek to assess treatment-free and overall survivals. They find that Hevylite® is a new and reliable marker for monitoring response to therapy and for accurately monitoring progression in WM, although it is still under investigation; Hevylite® might become the reference technique to monitor the IgM M-spike protein in years to come.

Background: Measurement of serum M-spike is used to determine response to therapy and treatment-free survival in Waldenström's Macroglobulinemia (WM), however, its resolution on serum protein electrophoresis (SPEP) can make accurate measurement difficult. The same applies to total IgM quantification by nephelometry (IgMneph) which inherently includes monoclonal and polyclonal immunoglobulins. IgM levels by either technique do not accurately reflect tumor load or prognosis in WM. There is a need to identify new markers that reflect disease burden and correlate with patients'outcomes. Hevylite measures IgMkappa and IgMlambda separately, and might provide true

quantitative measurement of the IgM M-spike. We sought to determine whether Hevylite® value can be used as a reliable marker for response to therapy in WM as compared to the M-spike measurement and to assess treatment free and overall survivals. Methods: The study was conducted in a series of 86 WM patients [71 at diagnosis and 15 at relapse], of whom 10 patients with WM were homogeneously treated at frontline in the multicentric Phase III trial, chlorambucil versus fludarabine that included WM. All serum samples were collected prior to treatment and were kept frozen since collection. Responses included partial response (PR) or better, confirmed at 2 consecutive values. Hevylite® measurements were made at The Binding Site Ltd, Birmingham, UK. A normal range was produced from normal (blood donor) sera (n=120), median (and 95%ile ranges) were; IgMkappa 0.634g/L (0.29-1.82), IgMlambda 0.42g/L (0.17-0.94), IgMkappa / IgMlambda ratio 1.6 (0.95-2.3). For ease of comparison, we have studied the clonal IgM hevylite, expressed as IgMi HL and the IgM Hevylite® ratios expressed as the involved monoclonal immunoglobulin / uninvolved polyclonal immunoglobulin (IgM HLR). Results: The median age was 66.7 years, Male/Female ratio was 1.77, and 51.2 % patients had WM-ISS score 3. The median (min-max) M-spike level was 20.6 g/L (3.2-90), IgMneph was 19.4 (2.4-87), the median IgM HLR ratio was 100 (2.59-2850) and the median IgMi HL level was 21.9 (1.94-126) g/L. The IgMi HL values correlated well with the M-spike (intra class correlation (icc) coefficient=0.48 [0.31; 0.60]) shown on the Bland-Altman plot left panel, and with the IgM neph (icc=0.74 [0.52; 0.86]), right panel of the attached figure. The IgM HLR also correlated to the M-spike (r=0.44, p<10-5) and the IgMneph (r=0.52, p<10-5), but on a lesser extent. The high IgMi HL level did not correlate to hemoglobin level, platelet count, beta-2 microglobulin and age, as for the IgM HLR in our study. The median IgMi HL did not vary significantly across ISS subgroups. The response rate was 60% at 14 months and 40% were stable (including minor disease) on the 10 WM homogeneously treated. The response rates and stable diseases were 40% and 60% using IgMneph, and 50% and 50% using IgMi HL, respectively. The concordance between IgMi HL with M-spike was quite good (k=0.61, p=0.13). The median time to response was similar across the 3 IgM techniques, 10.4 months as per protocol as compared to 12.9 months with IgMneph, and 11.8 months using IgMi HL. With a median follow-up of 45.7 months [40.7; 53.9], 50% of patients had a progression in the protocol, with a median time to progression (TTP) of 25.2 months. The progression rate was 66% using IgMi HL and 50% using IgMneph. The median TTP was similar with IgMi HL and IgMneph, 23.1 months and 13.8 months (p=NS), respectively. Similar results were observed with the median time to next treatment, 4.43 months, 10.9 months and 10.9 months, respectively (p=NS). Overall, 10 patients died, the median Overall Survival (OS) was not reached, the 5 year survival was 83.7% [73.6; 95.1]. The M-spike level by SPEP, as for the IgMi HL and IgMneph, did not predict for OS. Conclusion: Hevylite® is a new and reliable marker for monitoring response to therapy and to accurately monitor progression in WM, although still under investigation. The preliminary data we and others have obtained encourage us to further monitor the impact of this marker in larger studies, especially clinical trials, in WM. Hevylite® might become the reference technique to monitor the IgM M-spike protein in years to come.

Immunoglobulin Free Light Chain (FLC) and Heavy Chain/Light Chain (HLC) Assays – Comparison with Electrophoretic Responses in Multiple Myeloma (MM)

Parameswaran Hari, Marcelo C. Pasquini, Brent R. Logan, Edward A. Stadtmauer, Amrita Krishnan, Alan Howard, Sairah Alvi, Stephen Harding, Shelly L. Carter, Vincent Rajkumar, Edwin P. Alyea III, Muzaffar Qazilbash, Ginna G. Laport, David G. Maloney, Sergio Giralt and David H. Vesole.

Oral and Poster Abstracts: Myeloma - Biology and Pathophysiology, excluding Therapy: Poster II

Time: 6:00 PM-8:00 PM **Location: Hall GH**
Abstract No.: 2877 **Session: 651**

In order to assess the prognostic impact of free light chain (FLC) assays and to correlate them with electrophoretic/ immunofixation assessment, the authors analyze 497 stored serum samples from patients enrolled in the Blood and Marrow Transplant Clinical Trials Network 0102 clinical trial, sponsored by the NHLBI and NCI, of tandem autologous (autoHCT) vs. tandem autoHCT- allogeneic. The authors find that FLC ratio normalization had no impact, suggesting that stringent complete response criteria may need further validation.

FLC assay measures circulating unbound kappa and lambda light chains and is of diagnostic and prognostic value in plasma cell disorders. Normalization of FLC ratio is considered a higher level of complete response (CR) in MM but this has not been well validated prospectively. HLC is a novel antibody based assay that targets the unique junctional epitopes between the heavy chain and light chain constant regions of intact immunoglobulin (Ig) molecules. It separately measures in pairs the light chain types of each immunoglobulin class generating ratios of monoclonal Ig/background polyclonal Ig concentrations (i.e IgGκ/IgGλ, IgAκ/IgAλ and IgMκ/IgMλ), potentially simplifying assessment of monoclonal protein response. To assess the prognostic impact of these assays and to correlate them with electrophoretic/immunofixation (SPE/IFE) assessment, we analyzed 497 stored serum samples from patients enrolled in the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0102 clinical trial, sponsored by the NHLBI and NCI, of tandem autologous (autoHCT) vs. tandem autoHCT- allogeneic (alloHCT). Samples were collected prior to the first autoHCT and analyzed for Freelite® (FLC) and Hevylite® (HLC) at The Binding Site Ltd, Birmingham, UK. Corresponding disease status determination was centrally performed by an expert data review committee using uniform response criteria and correlated with FLC and HLC results. HLC remission was defined as normalization of composite heavy and light chain ratios across all 3 measured heavy/light chain pairs or the normalization of clonal isotype with normal ratios of uninvolved pairs. The demographics of 497 patients with HLC/FLC samples at baseline were concordant with the main study and showed similar patient proportions from the 2 study arms. Of the 211 patients with baseline SPE response better than or equal to a very good partial response (>VGPR), 188 also had an HLC

remission (Sensitivity=89%). Comparison of the HLC remission with the >VGPR disease state also identified a specificity of 52%, positive predictive value (PPV) of 58% and a negative predictive value (NPV) of 87%. Similarly, all 56 patients in complete remission (CR) by SPE/IFE were in HLC remission. Compared with conventional CR assessment, sensitivity of HLC remission was 100%, specificity 39%, PPV and NPV values of 17% and 100% respectively. FLC remission correlated with >VGPR disease state had a sensitivity of 47%, specificity of 81%, and a PPV and NPV of 64% and 67% respectively. Multivariate models for post transplant progression-free survival (PFS) indicated that baseline disease response (>VGPR vs. partial remission (PR) or<PR) was associated with longer PFS. Adjusted models including baseline response, MM stage, and study arm were used to compare the predictive utility of HLC and FLC assays. There was a lower risk of treatment failure (HR 0.74, p=0.02) and superior PFS for patients who achieved an HLC remission. When stratified by baseline disease response states, there was no additional prognostic impact for HLC remissions on PFS. Normalization of FLC ratio among patients with >VGPR disease state did not impact PFS (HR 0.96, p=0.83). Abnormal HLC after induction therapy has a high negative predictive value (100%) for identifying patients not achieving CR by uniform response criteria and is also associated with shorter PFS after transplant. FLC ratio normalization had no impact suggesting that stringent CR criteria may need further validation.

Serum Heavy/Light Chain and Free Light Chain Measurements Provide Prognostic Information, Allow Creation of a Prognostic Model and Identify Clonal Changes (clonal tiding) Through the Course of Multiple Myeloma (MM).

Heinz Ludwig, Jeffrey Faint, Niklas Zojer, Arthur R. Bradwell, Philip Young, Dejan Milosavljevic, Wolfgang Hübl, and Stephen Harding.

Oral and Poster Abstracts: Myeloma - Biology and Pathophysiology, excluding Therapy: Poster II

Time: 6:00 PM-8:00 PM **Location: Hall GH**

Abstract No.: 2883 **Session: 651**

In order to evaluate the prognostic value of the heavy light chain (HLC) ratio, the authors construct a two tiered prognostic model employing the HLC and free light chain (FLC) tests, and use these assays to analyze the clonal tide in patients with myeloma (MM). They find that a highly abnormal HLC ratio correlates with shorter survival and that a risk-stratification model combining HLC and FLC ratio reveals marked discriminative power; monitoring patients with FLC and HLC assays shows significant changes in clonal protein production as an indication of a major clonal tide in about 10% of MM patients.

In multiple myeloma (MM), increasing evidence indicates progressive clonal evolution A novel polyclonal immunoassay specific for the different light chain types of intact immunoglobulins (Ig) (heavy/light chain assays; HLC) and the serum free light chain (FLC) test enable measurement of changes in the production of clone specific Ig and of the non-involved polyclonal Ig of the same isotype. By calculating the HLC ratio, the relationship between clonal and non clonal plasma cells can be assessed. Here we evaluate the prognostic value of the HLC ratio, construct a two-tiered prognostic model employing the HLC and FLC tests, and use these assays to analyze the clonal tide in patients (pts) with MM. 103 previously untreated patients with MM were enrolled (35 IgGκ, 17 IgGλ, 29 IgAκ, 22 IgAλ). ISS stage I: 39 (38%), stage II: 42 (41%), stage III: 22 (21%) patients. Median age: 66 years (range 32-86). 82 patients with a minimum of 5 serum samples were followed for a median of 36 months (range: 57 days -133 months). Serum FLC and HLC (IgGk/IgGl, IgAk/IgAl) measurements were made using polyclonal antisera assays (Freelite®, The Binding Site Ltd, Birmingham, UK. and, Hevylite®, The Binding Site Ltd, Birmingham, UK). Serum protein electrophoresis and immunofixation were conducted on a SEBIA Hydrasys II platform. Survival analysis was performed using the SPSS v 18 programme. Median survival of the entire patient cohort was 53.6 months. When patients were stratified according to their presentation HLC ratios being moderately abnormal (0.022 - 45; n=51) or highly abnormal (<0.022 or >45; n=52), survival was significantly shorter in those with highly abnormal ratios (median 32.1 months vs. median not reached, HR: 2.07, CI 1.15 – 3.75, p=0.016). The survival rates at 5 years were 33.4% for the former and 58.9% for the latter group (p=0.01). For patients with a highly abnormal FLC ratio (<0.1 or >30) a statistically non-significant tendency for shorter survival was noted (40.8 months vs. median not reached, HR: 1.72, CI: 0.93 – 3.17, p=0.08) compared to those with less abnormal FLC ratios (0.1 - 30). A risk stratification prognostic model with highly abnormal HLC and FLC ratios as risk factors at presentation was developed. Overall survival was significantly different between patients with both, highly abnormal HLC and FLC ratios, or only one, or none of these risk factors (p=0.01). The median was not reached in patients with 0 or 1 risk factor and was 29.2 months in those with 2 risk factors. The respective five year survival rates were 67.4%, 50.0%, and 23.3% (0 risk factor, HR: 1, 1 vs. 0 risk factor, HR: 1.76 CI: 0.71 – 4.33, p=0.22, 2 vs. 0 risk factor, HR: 3.69, CI: 1.45 – 9.44 for 2 risk factors, p=0.006). The comparison of FLC and HLC values over the follow-up period revealed concordance of changes in 75 patients (91.5%). In 1 patient after 78 days a >50% reduction in dFLC (and FLC ratio) indicated a partial response, whereas HLC ratios (and IgGk concentrations) showed no response; this indicates the existence of clones with different sensitivity to MM therapy. FLC escape was noted in 1 patient with increasingly abnormal free FLC values while HLC ratios remained stable. In 4 patients, increasingly abnormal HLC ratios at the same time as FLC values were stable or normalising indicated outgrowth of clones producing intact Ig only. One additional patient showed an increasingly abnormal HLC ratio due to subtle suppression of the polyclonal Ig while the monoclonal concentration remained constant. Conclusion: Highly abnormal HLC ratio correlates with shorter survival and a risk-stratification model combining HLC and FLC ratio revealed marked discriminative power. Monitoring patients with FLC and HLC assays showed significant changes in clonal protein production as an indication of a major clonal tide in about 10% of MM patients.

Extensive Bone Marrow Infiltration and Abnormal Free Light Chain Ratio Identifies Patients with Smoldering Multiple Myeloma at High Risk for Progression to Symptomatic Disease

Efstathios Kastritis, Lia A. Moulopoulos, Maria Gkotzamanidou, Dimitra Gika, Maria Roussou, Maria Gavriatopoulou, Magdalini Migkou, Evangelos Eleutherakis-Papaiakovou, Evangelos Terpos, and Meletios Athanasios Dimopoulos.

Oral and Poster Abstracts: Myeloma - Biology and Pathophysiology, excluding Therapy: Poster III

Time: 6:00 PM-8:00 PM **Location: Hall GH**
Abstract No.: 3926 **Session: 651**

In order to evaluate previously recognized risk factors and study patterns of progression, the authors analyze a series of patients with smoldering multiple myeloma (SMM). In their patient population, they find that the three-year probability of progression to symptomatic MM is about 20%, but that there is a subgroup of patients with extensive bone marrow (BM) infiltration (≥60%) and highly abnormal free light chain ratio who have a substantial risk of progression to symptomatic disease within the first two years from the diagnosis.

Asymptomatic/smoldering multiple myeloma (SMM) is a proliferative plasma cell disorder characterized by a substantial risk of progression to symptomatic MM. According to current recommendations, patients with SMM should be followed without treatment until they develop symptomatic disease. However, the risk of progression to symptomatic MM varies between different series and for individual patients; thus, significant effort is needed in order to identify factors that could discriminate those who are at high risk for progression. Such patients should be followed closer and should be considered candidates for clinical trials. In order to evaluate previously recognized risk factors and study patterns of progression we analyzed our series of patients with SMM, who have been diagnosed and followed in the Department of Clinical Therapeutics in Athens, Greece. SMM was defined as serum monoclonal (M) protein (IgG or IgA) level of ≥3 g/dL and/or bone marrow plasma cells ≥10%, absence of end-organ damage, such as lytic bone lesions, anemia, hypercalcemia, or renal failure, that can be attributed to a plasma cell proliferative disorder (IMWG criteria, *Br J Haematol* 2003;121:749-57). Progression to symptomatic MM was defined as per the IMWG proposed criteria. We analyzed 95 patients with SMM, 53% of whom were females, 70% had IgG heavy chain, 22% had IgA, 5% had a biclonal SMM and 3% had light chain only SMM, while 65% had a kappa light chain and 35% a lambda light chain. Median infiltration by clonal plasma cells in BM trephine biopsy was 20% (range 10-90%), 10% of patients had ≥60% clonal plasma cells in BM biopsy. Fifty patients had MRI of the spine at the time of diagnosis of SMM and 19.5% had an abnormal pattern of BM infiltration (diffuse, focal or variegated pattern). In patients with available bone marrow immunohistochemistry data, 61% had clonal plasma positive for CD56, 17% for CD20 and 19% for cyclin D1. The median follow up of the cohort was 27 months (range 1-253 months) and 23 (24%) patients have progressed to symptomatic MM. The 1-year, 2-year, and 3-year cumulative probability of progression was 7%, 12%, and 20% respectively. Nine patients (9.5%) progressed within the first two years from the diagnosis of SMM. All these patients had an M-protein of ≥1 g/dl (10 g/L), 67% had bone marrow plasma cells >60% and 80% had an abnormal MRI pattern of BM infiltration. The 3-year probability of progression to symptomatic MM was 4%, 18%, and 87% for patients with <20%, 20-59%, and ≥60% clonal plasma cells in bone marrow biopsy (P<0.001). The 2-year probability of progression to symptomatic MM was 0%, 13%, and 60% for patients with <20%, 20-59%, and ≥60% clonal plasma cells in BM biopsy (P<0.001). Patients with significantly abnormal free light chain ratio (either kappa/lambda ≥8 or kappa/lambda ≤0.125, according to Dispenzieri et al, *Blood* 2008;111:785-9) had a 3-year probability of progression to symptomatic MM of 41% vs. 15% (p=0.07). There was no significant difference in the risk of progression to symptomatic MM for patients with IgA vs. IgG MM. In multivariate analysis, abnormal FLC ratio less than 0.125 or more than 8 (HR: 6.4, 95% CI 1.3-34.5 p=0.032) and BM clonal plasma cells infiltration ≥60% (HR: 23, 95% CI 5-125, p<0.001) were independent risk factors for progression to symptomatic MM. Progression to symptomatic MM was manifested by the development of anemia in 52% of patients who progressed to symptomatic MM, development of lytic bone lesions or pathologic fracture in 48%, an increase of serum creatinine to ≥2 mg/dl in 13%, development of a soft tissue plasmacytoma in 4% and development of hypercalcemia in 4%. In conclusion, in our series of patients, the 3-year probability of progression to symptomatic MM is about 20%, but there is a subgroup of patients with extensive bone marrow infiltration (≥60%) and highly abnormal FLC ratio, who have a substantial risk of progression to symptomatic disease within the first two years from the diagnosis of SMM. These high-risk patients may also have other features such as abnormal MRI of the spine. Patients at high risk for progression should be considered for clinical trials evaluating the role of treatment before the development of symptomatic disease, which in most cases is manifested with anemia and/or lytic bone disease or pathologic fractures.

An International Study of High Cut-off Hemodialysis for the Management of Myeloma Kidney

Colin A. Hutchison, Anne Bevins, Graham Mead, and Mark Cook.

Oral and Poster Abstracts: Myeloma - Therapy, excluding Transplantation: Poster III

Time: 6:00 PM-8:00 PM **Location: Hall GH**
Abstract No.: 3974 **Session: 653**

An early reduction in serum free light chains (FLC) improves outcomes for patients with myeloma kidney. In this study, the authors seek to assess how high cut-off (HCO) dialysers are being used internationally to achieve this improved outcome. The authors find that reducing FLC in patients with myeloma kidney is associated with increased levels of dialysis independence, and this study adds further evidence that a combination of chemotherapy and FLC removal by HCO hemodialysis improves patient outcomes following acute kidney injury secondary to MM.

Background: An early reduction in serum free light chains (FLC) improves outcomes for patients with myeloma kidney. The purpose of this study was to assess how high cut-off (HCO) dialysers are being used internationally to achieve this target. Methods: Data was collected for 54 patients, from 18 centers in 10 countries. Clinical presentation and treatment parameters, including details of removal of FLCs with high cut off hemodialysis and chemotherapy treatment, were captured using a web-based collection database. Demographics: All patients were Caucasian, median age of 65 years (range 43-81). Median biochemistry at presentation was: GFR of 8mls/min/1.73m^2 (1-27), creatinine 633.5μmol (168-2263); calcium 2.3mmol/L (0.91-3.83); albumin 34g/L (14-46) and β2M 9.45mg/L (0-55.7). Baseline monoclonal κ and λ FLCs levels were: 5070mg/L (range 2250-20200) and 4200mg/L (range 300-13300), respectively. Of the patients who received a renal biopsy, 81% had myeloma kidney as their primary diagnosis. For initial chemotherapy prescriptions: 78% received bortezomib and 34% received thalidomide. 68.75% of the patients were treated with the Theralite HCO dialyzer; the other 31.25% received treatment with the HCO1100 dialyzer. There was a total of 626 HCO dialysis sessions recorded, with each patient receiving on average 13 sessions each (median, range 3-35) treatments per patient. Of the 54 patients, only 3 were treated with HDF. Results: 73.2% of patients demonstrated a decreased serum FLC level over the course of treatment, with 86.7% of these patients demonstrated decreased levels by day 12. The median FLC reduction achieved was 72.96% (15.09-99.62%) by day 12 and 93.03% (40.23-99.96%) by the last dialysis treatment. There was no difference in the percentage FLC reduction achieved between bortezomib (median: total 94.09%, day 12 79.14%) and thalidomide (median: total 77.65%, day 12 66.51%) treatment groups (total $p=0.179$, day 12 $p=0.300$). FLC removal was significantly increased in patients receiving Theralite treatment over those receiving HCO1100 at both day 12 ($p=0.030$) and by the end of treatment ($p=0.031$). Dialysis independence occurred in 68.2% of patients, median time 32 days (10-249). Patients who became independent of dialysis had significantly greater reductions in serum FLC by day 12 ($p=0.032$). No significant adverse events related to the study device were reported. Conclusion: Reducing FLC in patients with myeloma kidney is associated with increased levels of dialysis independence. This study adds further evidence that a combination of chemotherapy and FLC removal by HCO hemodialysis improves patient outcomes following acute kidney injury secondary to MM.

Serum Free Light Chain Ratio in Distinguishing Smoldering Multiple Myeloma from Active Multiple Myeloma

Jeremy T. Larsen, Shaji Kumar, and S. Vincent Rajkumar.

Oral and Poster Abstracts: Myeloma - Biology and Pathophysiology, excluding Therapy: Poster III

Time: 6:00 PM-8:00 PM **Location: Hall GH**
Abstract No.: 3948 **Session: 651**

This retrospective analysis of 586 patients with newly diagnosed smoldering myeloma finds that development of a free light chain (FLC) ratio >100 is associated with increasing disease burden, and in this study behaved in a malignant fashion rather than a precursor state. The authors conclude that the FLC is a simple and useful predictor of progression to MM in smoldering myeloma, and that patients with FLC ratios of <0.01 or >100 within the first two years of smoldering myeloma diagnosis should be monitored especially closely; future studies are needed to determine optimum cutoffs for FLC ratio to where a change in definition of MM could be considered.

Background: Smoldering multiple myeloma (SMM) is an asymptomatic precursor disease of multiple myeloma (MM), and is defined by excess bone marrow plasma cells and monoclonal protein without evidence of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions [CRAB]). The identification of SMM patients with more aggressive underlying disease remains a challenge. We hypothesize that SMM is a clinical entity comprised of both premalignant, high-risk MGUS and early MM in transition to malignant disease, which may be differentiated with the use of the serum FLC (FLC) ratio. Methods: This was a retrospective analysis of 586 patients with newly diagnosed SMM from 1970-2010 with available stored serum samples around the time of diagnosis to be utilized for quantification of FLC ratios. SMM was defined by the International Myeloma Working Group (IMWG) 2003 definition; serum M-protein $\geq$ 3 g/dL and/or $\geq$ 10% bone marrow plasma cells with no evidence of CRAB features. The immunoglobulin FLC assay (The Binding Site Ltd, Birmingham, UK) was used for testing. The FLC ratio was calculated as κ/λ (reference range 0.26-1.65). The involved/uninvolved FLC ratio was recorded to simplify the reporting of data. Receiver Operating Characteristics (ROC) curves were created to assess the ability of the FLC ratio to discriminate patients who progressed to

symptomatic MM in the first 2 years or at any point during follow-up versus patients without evidence of progression. Patients with less than 24 months follow-up without progression were censored. The optimal diagnostic cut-point for FLC involved/uninvolved ratio to identify patients with progressive disease from the ROC curve was >88.6 (equivalent to <0.011 or >88.6). For ease of clinical application, the optimal value for involved/uninvolved FLC ratio was rounded to >100. Time to progression (TTP) from date of the initial FLC to active MM was calculated using Kaplan-Meier analysis and compared to patients with a high (>100) and low (<100) involved/uninvolved FLC ratio at time of SMM diagnosis. TTP within 24 months of the initial FLC was also calculated. Results: During the study period, 54% of patients progressed to active MM. On ROC analysis, a cut-point of >100 corresponded to a sensitivity of 25% (95% CI, 20.5-30.4) and specificity of 99.3% (97.3-99.9), with positive likelihood (+LR) ratio of 33.9 (38.1-41.0), negative likelihood ratio (-LR) of 0.75 (0.2-3.0), positive predictive value (PPV) of 97.6 (91.5-99.7) and negative predictive value of 53.0 (48.5-57.4). Using the ROC to assess progression to MM within 24 months (Figure 1), sensitivity was 29.6% (23.5-36.4), specificity 94.5% (91.7-96.5), +LR 5.36 (4.3-6.6), -LR 0.75 (0.5-1.1), PPV 85.8 (77.7-91.8), and NPV 54.3 (49.8-58.9). Median TTP to active MM in the FLC >100 group was 15 months (9-17) versus 52 months (44-60) in the FLC <100 group (p<.0001). In the FLC ratio >100 group, progression at 1 year was 47%, 76% at 2 years, and 90% at 3 years. Only 25% of the FLC <100 patients had progressed at 2 years. The most common progression event was bone disease (42%), followed by anemia (26%), renal impairment (23%), and hypercalcemia (5%). Conclusion: Elevation of the FLC ratio >100 (or <0.01) is highly specific for the future development of active MM, with 76% of these patients developing end-organ damage requiring therapy within 2 years. Risk of transformation to MM in the FLC <100 group was similar to previously reported rates of 10% per year for the first 5 years. Development of an FLC ratio >100 is associated with increasing disease burden and in this study behaved in a malignant fashion rather than a precursor state. The FLC is a simple and useful predictor of progression to MM in SMM, and patients with FLC ratios of <0.01 or >100 within the first 2 years of SMM diagnosis should be monitored especially closely. Future studies are needed to determine optimum cutoffs for FLC ratio to where a change in definition of MM could be considered.

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