ABSTRACT E- BOOK

INTERNATIONAL KIDNEY & MONOCLONAL GAMMOPATHY

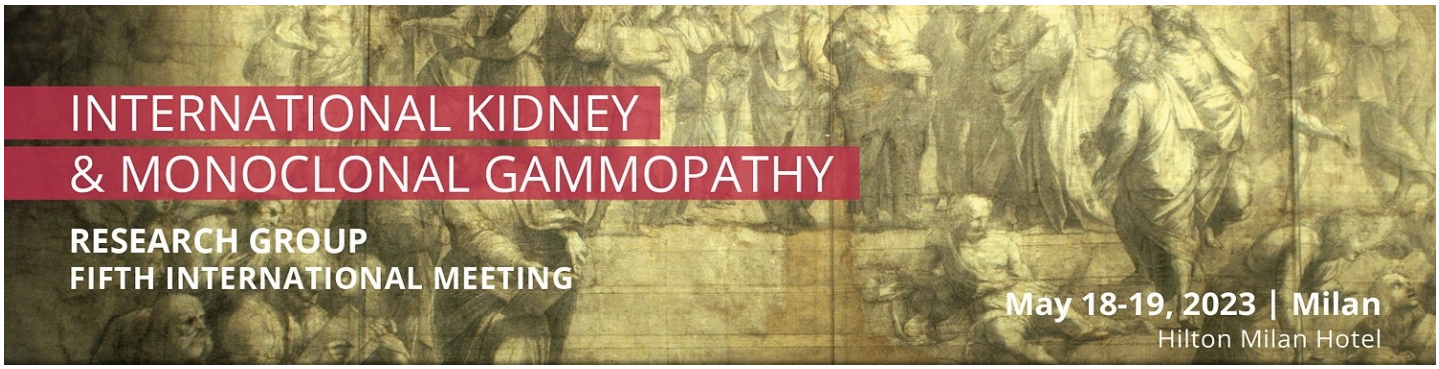
RESEARCH GROUP
FIFTH INTERNATIONAL MEETING

May 18-19, 2023 | Milan
Hilton Milan Hotel

IKMG

International Kidney & Monoclonal
Gammopathy Research Group

Index



Abs C01

2. Diagnosis of MGCS

HOW TO RULE OUT MGRS IN PATIENTS WITH PROLIFERATIVE GLOMERULONEPHRITIS WITH MONOCLONAL IMMUNOGLOBULIN DEPOSITS?

V. Javaugue*, V. Pascal*, S. Bender*, A. Rinsant*, J.m. Goujon*, G. Touchard*, F. Bridoux*, C. Sirac*

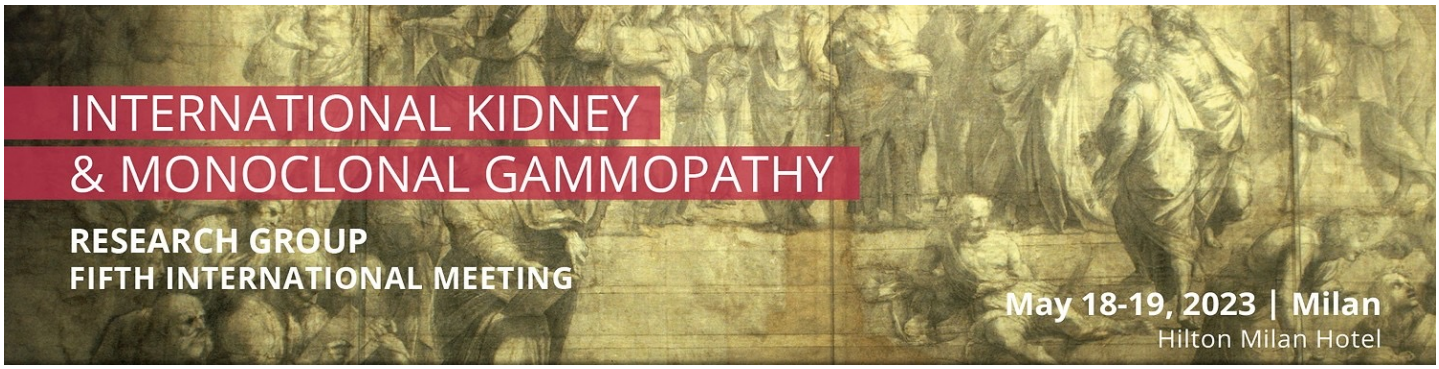
**French National Reference Centre for AL Amyloidosis and Other Monoclonal Ig Deposition Diseases, University Hospital of Poitiers and Limoges, France.*

The pathophysiological mechanisms of proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) are still largely unknown. Only 30% of PGNMID cases have a detectable circulating monoclonal immunoglobulin (Ig) and a bone marrow corresponding clone.

We reviewed a French cohort of PGNMID with particular focus on hematological characteristics. A high-throughput sequencing assay from bone marrow and/or blood mRNA encoding immunoglobulins (RACE-RepSeq) was used to detect the underlying clone.

Seventy-one patients (M/F ratio=1.6, median age 59 years) were included. At diagnosis, 73% had renal insufficiency (median serum creatinine=1.7 mg/dL). All patients had proteinuria, with nephrotic syndrome in 59% and microscopic hematuria in 85% of cases. No patient had extra-renal manifestations. By light microscopy, kidney biopsy revealed membranoproliferative glomerulonephritis (74%), mesangial glomerulonephritis (14%) or membranous glomerulonephritis (12%). By immunofluorescence, deposits stained for IgG in 55 cases (mostly IgG3κ), IgM in 7 cases, IgA in 4 cases or light chain (LC) only in 5 cases. Serum and/or urine immunofixation was positive in 26 cases (37%). An underlying clone was found in 21 cases (30%), using bone marrow or blood flow cytometry analysis. The clonal detection rate was particularly low in IgG3κ-PGNMID (5%). The nature of the clone differed with PGNMID subtype: lymphoplasmacytic in IgM-PGNMID, and plasmacytic in IgA/LC-PGNMID. RACE-RepSeq analysis failed to detect a bone marrow or blood clone in 32/40 cases (IgG3-PGNMID, n=29; IgA-PGNMID, n=3). To confirm the absence of monoclonal Ig deposits in IgG3κ-PGNMID patients, we performed immunofluorescence analysis on kidney biopsy samples from 5 IgG3κ-PGNMID patients without a detectable clone and 1 IgG1κ-PGNMID with detectable clone using anti-Vκ antibodies. Interestingly, in IgG3κ-PGNMID patients without detectable clone, positive staining was observed with anti-Vκ1, anti-Vκ2, anti-Vκ3 +/- anti-Vκ4 antibodies, whereas deposits stained only for Vκ2 in the IgG1κ-PGNMID patient who had a bone marrow Vκ2clone by RACE-RepSeq analysis.

These results suggest that PGNMID is a heterogeneous medical condition and that some cases might involve oligoclonal production of nephrotoxic Ig restricted to the IgG3κ isotype. Such cases should no longer be classified as MGRS.



Abs C02

2. Diagnosis of MGCS

RNA-BASED IMMUNOGLOBULIN REPERTOIRE SEQUENCING IS A USEFUL TOOL FOR THE MANAGEMENT OF MONOCLONAL GAMMOPATHY OF CLINICAL SIGNIFICANCE

S. Bender 1-4, V. Javaugue 1-2, M. Roussel 1-3, K. Queru 1-3, E. Desport 1-2, G. Martinez-rivas 1, F. Bridoux 1-2, A. Jaccard 1-3, C. Sirac 1, V. Pascal 1-4

1 French National Reference Centre for AL Amyloidosis and Other Monoclonal Ig Deposition Diseases, Universitary Hospital 2 Nephrology Department, Universitary Hospital

3 Hematology and Cellular Therapy Department, Universitary Hospital

4 Immunology Laboratory, Universitary Hospital

We have recently developed a high-throughput sequencing assay from bone marrow and/or blood mRNA encoding immunoglobulins (RACE-RepSeq). This technique provides both full-length V(D)J region of the monoclonal immunoglobulin and the dominant immunoglobulin repertoire, allowing analysis of mutational patterns, immunoglobulin variable gene frequencies, diversity due to somatic hypermutation and bi- or multiclonality.1,2 We analyzed by RACE-RepSeq bone marrow and/or blood samples from patients with various types of diseases, including AL amyloidosis (n=120), POEMS syndrome (n=64), PGNMID (n=40), monotypic fibrillary glomerulonephritis (n=3) and IgA nephropathy with lambda restriction (n=4).

In patients with clinically proven AL amyloidosis, a bone marrow clone was found in 118/120 cases (98%) including those with undetectable clones by other classical techniques. Overall, 67.5% of the patients were lambda. Regarding lambda light chain amyloidosis, 27% (n=22) were IGLV2-14, 21% (n=17) IGLV6-57, 12.5% (n=10) IGLV1-44 and all others below 10%. Regarding the kappa AL patients, IGKV gene frequencies of use were as followed: 29.5% (n=10) for IGKV1-33, 20.5% (n=7) IGKV1-39, 14.5% (n=5) IGKV1-5 and the other below 10%. In comparison with control light chain repertoires, and as previously shown, we observed a specific restriction of use for IGLV6-57 and IGLV1-44 genes. Although frequently found in AL amyloidosis, IGLV2-14 segment is already preferentially use in controls. For κpatients, IGLV1-33, IGLV1-39, and IGLV1-5 frequencies of use seems higher compared with controls. VLAmy-Pred tool predicted only ~60% of amyloidogenic sequences and ~20% of IGK sequences were predicted to be N-glycosylated with the NetNGlyc tool. 6% of patients presented with two or more monoclonal LC sequences.

In POEMS patients, the diagnosis was certain for 47 of them and possible for 17 of them. A bone marrow clone was found in 50/64 (78%) with lambda light chain restriction, including 36 certain and 14 possible cases. Regarding IGLV gene usage, 72% of the patients (n=36/50) were IGLV1-44 (n=22, 44%), IGLV1-40 (n=10, 20%), or IGLV1-36 (n=4, 8%), all with an IGLJ3*02 restriction. 28 patients had the characteristic mutational patterns in the CDR1/FR2 region (n=18 for IGLV1-44 and n=10 for IGLV1-40).

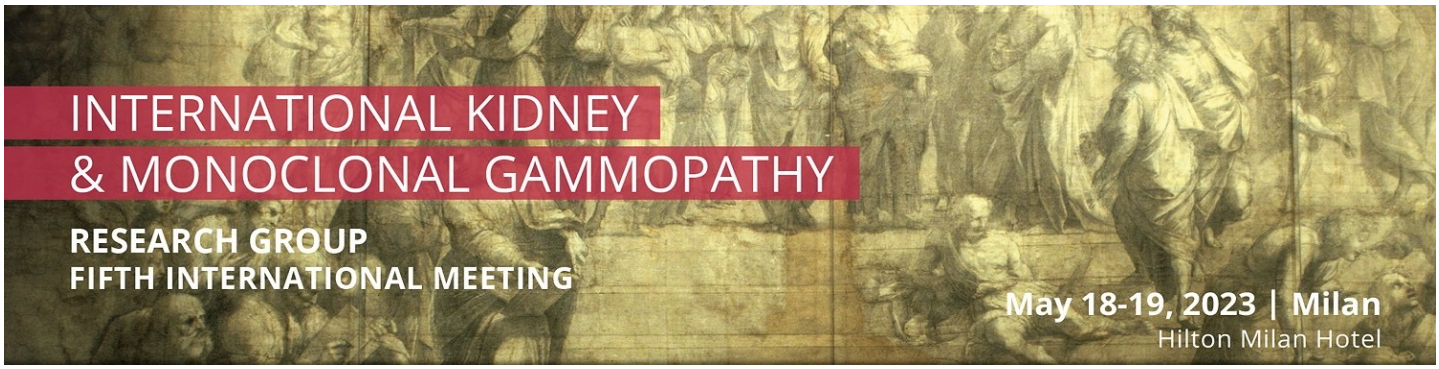
In PGNMID, a bone marrow clone was found in 8/40 (20%), including 2 cases with negative serum/urine immunofixation. The clonal detection rate differed with PGNMID subtype and was particularly low in IgG3kappa-PGNMID (5%). No clone was found in patients with monotypic fibrillary glomerulonephritis and IgA nephropathy with lambda restriction.

Our results indicates that RACE-RepSeq is a sensitive method to detect small B/plasma cell clones in patients with various types of MGCS. This tool appears also useful to rule out the monoclonal origin of certain renal diseases in which immunofluorescence studies lack enough sensitivity to differentiate between monoclonal and oligoclonal Ig deposits, such as PGNMID, monotypic fibrillary glomerulonephritis or IgA nephropathy with lambda restriction.

Refs

1.Immunoglobulin variable domain high-throughput sequencing reveals specific novel mutational patterns in POEMS syndrome. Bender S et al, Blood. 2020 May 14;135(20):1750-1758.

2.RNA-based immunoglobulin repertoire sequencing is a new tool for the management of monoclonal gammopathy of renal (kidney) significance. Javaugue V et al, Kidney Int. 2022 Feb;101(2):331-337.



Abs C03

1. Basic science

AN ANTIBODY AND SITE-DIRECTED MUTAGENESIS-BASED STRATEGY TO UNDERSTAND IMMUNOGLOBULIN LIGHT CHAIN AMYLOID AGGREGATION

L. Del Pozo-yauner1, F. J. Rodriguez-alvarez2, R. Ruiz-zamora2, V. Bellamkonda1, G.a. Herrera1, E.a. Turbat-herrera1,3, Y. Al Hilaly4,5, B. R. Alarcon- sanchez2, J. F. Chandomi2, B. Liu1, J. Arellanes-robledo6[^][/^], J. I. Perez-carreon2, L. Serpell4

1)Department of Pathology, University of South Alabama College of Medicine, USA

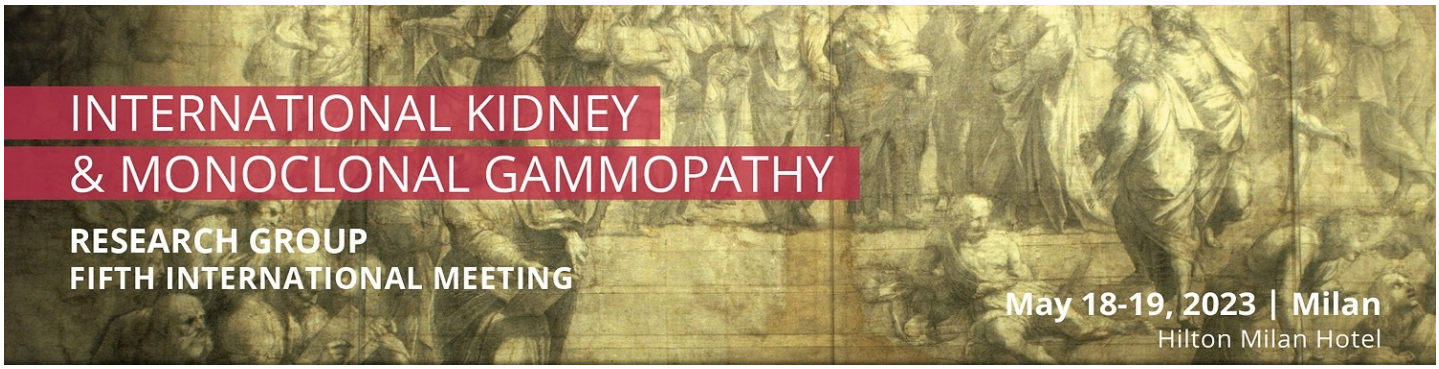
2) Instituto Nacional de Medicina Genómica, Mexico

3) Mitchell Cancer Institute, University of South Alabama College of Medicine, USA 4) School of Live Sciences, University of Sussex, UK

5) Chemistry Department, College of Science, Iraq.

6) CONACYT – Instituto Nacional de Medicina Genómica, México.

Previous studies suggested that the aggregation hotspots located in the CDR1, and the beta-strands B, D, and E are crucial for the mechanism of aggregation of the model protein 6aJL2. We anticipated that changes disrupting structural motifs that prevent these segments from engaging in edge-to-edge contacts are early events of the aggregation pathway of 6aJL2 protein. To test this hypothesis, we applied a strategy based on immunoassays with several conformation-sensitive antibodies and site-directed mutagenesis in positions that we predicted to play a key structural role in the stability of 6aJL2 native conformation. Ultrastructural analysis of the aggregates was performed with transmission electron microscopy with immunogold labeling (TEM-IGL). Site-directed mutagenesis by Asp showed that the aggregation hotspots identify in the CDR1 are critical for the mechanism of amyloid aggregation. In vitro amyloidogenesis was strongly inhibited in double and triple mutants targeting residues in this protein region. Dot-blot assays showed that mutations in structural key residues of the beta-strand A, such as Phe2, Pro7, and Pro15 make the beta-strand B more accessible to antibody recognition, which was associated with faster kinetics of fibrillogenesis. However, mutations by Asp in positions at the beta-strand B exerted fewer effects on in vitro fibrillogenesis, compared with mutations in the CDR1. Interestingly, mutation by Trp in positions flanking Cys23 inhibits the in vitro fibrillogenesis of 6aJL2, which suggest that conformational freedom around the highly conserved intradomain disulfide bond Cys23-Cys88 is a key requirement for the mechanism of aggregation. Dot-blot and TEM-IGL showed that the conformation-sensitive antibodies recognize both prefibrillar aggregates and amyloid-like fibrils formed by 6aJL2 protein, but not their native state. Dot blot assay revealed that conformational adjustments involving the loop spanning residues 40-60 occur early in the fibrillogenesis of 6aJL2 protein. As the aggregation proceeds, other protein segments become accessible to antibody recognition, which is consistent with previous studies based on a solid-state nuclear magnetic resonance that showed that the in vitro fibrillogenesis of 6aJL2 is accompanied by an extensive conformational conversion that involves the whole molecule. Our findings indicate that the highly amyloidogenic hotspot located in the CDR1 plays a central role in the aggregation mechanism of the 6aJL2 protein. The early phase of the in vitro fibrillogenesis of 6aJL2 is characterized by conformational changes involving the loop 40-60, as well as the beta-strand B and CDR1. These conformational are accelerated by incubating the protein at 37^{0}C with constant agitation, but also spontaneously occur in protein preparations stored at 4^{0}C for several weeks.



Abs C04

3. Treatment of MGCS

RENAL RESPONSE AND PROGRESSION CRITERIA FOR LIGHT CHAIN (AL) AMYLOIDOSIS

E Muchtar1, B. Wisniowski2, S. Geyer3, K. Dooley, G3. Palladini4, P. Milani4, G. Merlini4, S. Schönland5, K. Veelken5, U. Hegenbart5, A. Dispenzieri1, S. Kumar1, N. Leung1, E. Kastritis6, M. Dimopoulos6, M. Liedtke7, R. Witteles7, V. Sanchorawala8, R. Szalat8, H. Landau9, E. Petrlik9,

S. Lentzsch10, A. Coltoff10, J. Bladé11, Mt Cibeira11, O. Cohen2, D. Foard2, J. Gillmore2, H. Lachmann2, A. Wechalekar2, M. Gertz1

1Division of Hematology, Mayo Clinic

2National Amyloidosis Centre, University College London Medical School, Royal Free Hospital Campus

3Amyloidosis Research and Treatment Center, Fondazione IRCCS Policlinico San Matteo, and Department of Molecular Medicine, University of Pavia 4Division of Clinical Trials and Biostatistics, Mayo Clinic

4Medical Department V, Amyloidosis Center, University of Heidelberg

5Department of Clinical Therapeutics, National and Kapodistrian University of Athens

6Stanford Amyloid Center, Stanford University School of Medicine

7Section of Hematology and Oncology, Amyloidosis Center, Boston University School of Medicine, Boston Medical Center 8Division of Hematologic Oncology, Memorial Sloan Kettering Cancer Center

9Division of Hematology/Oncology, Columbia University Medical Center

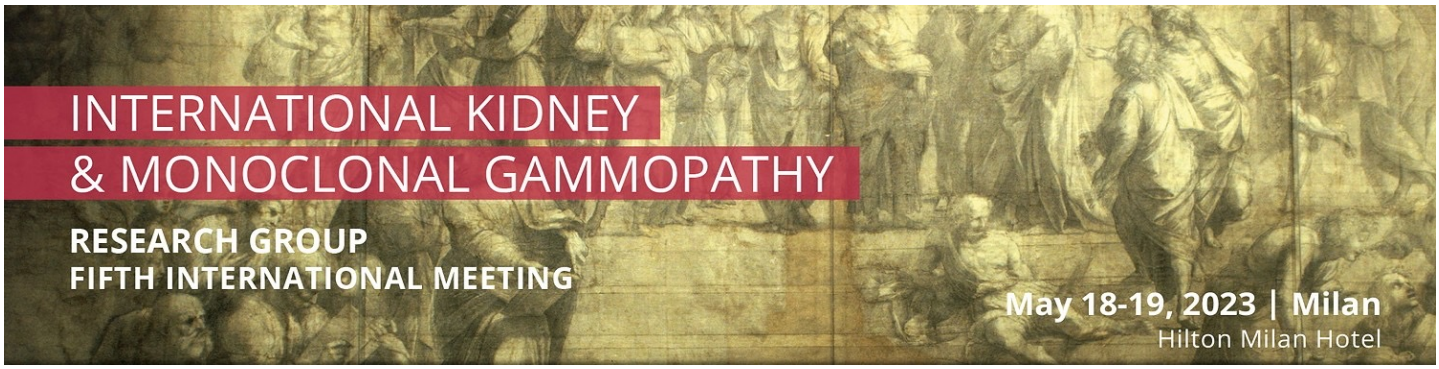
10Department of Hematology, IDIBAPS, Hospital Clinic, Barcelona

Introduction: Renal light chain (AL) amyloidosis manifests as proteinuria and/or renal failure and is associated with a risk of progression to renal replacement therapy (RRT) and death. Several studies suggest that a greater reduction in proteinuria following successful therapy improves outcomes.

Methods: Patients (n=732) with renal AL amyloidosis achieving at least hematological partial response and were evaluable for renal response were included. Four renal response categories were formulated based on the level of reduction in pretreatment 24-h proteinuria: complete response (renCR, proteinuria reduction ≤200 mg/24-h), very good partial response (renVGPR, >60% reduction in proteinuria from baseline level not meeting renCR), partial response (renPR, 31-60% reduction in proteinuria from baseline) and no response (renNR, ≤30% reduction in proteinuria from baseline). Renal response was assessed at landmarks (6, 12 and 24 months from treatment initiation) and at best renal response. eGFR progression was defined as a ≥25% decrease in eGFR. Cumulative incidence (CI) of RRT was defined as the proportion of patients who progressed to RRT from therapy initiation. Competing-risk analysis was used to assess the CI of RRT. Overall survival (OS) was calculated from time of therapy initiation until death from any cause or last follow-up. A time-dependent covariate Cox regression models for OS were performed, with longitudinal renal response assessment (fixed time and best renal response) included in these models.

Results: The median age was 63. The median baseline 24-h proteinuria and eGFR was 5.3 g/24-h and 72 mL/min/1.73m2, respectively. Renal stage I, II and III was assigned to 34%, 52% and 14% of patients, respectively. A reduction in 24-h proteinuria from baseline improved over time with a median percentage reduction of 34%, 50% and 71% at 6-, 12- and 24-month time points, respectively. The corresponding best renal response categories were 26.1%, 31.7%, 14.5% and 27.7% for renCR, renVGPR, renPR, and renNR, respectively. In a competing-risk analysis, the 5-year CI of RRT decreased with a deeper renal response as early as 6 months from therapy initiation (12%, 10%, 2.2%, and 0% for renNR, renPR, renVGPR, and renCR, respectively; P=0.006; Figure). Discrimination of CI of RRT by renal response category was maintained at 12- and 24-months and at best renal response. In all landmark time points, the 4-level renal response performed better than a 2-level response (using a 30% reduction cutpoint) in predicting CI of RRT, with a gradually improved performance between 6-month and 24-month time points. Patients who achieved a deeper renal response had longer survival, noted as early as 12 months from therapy initiation and at 24 months (estimated 5-year OS 90.8%, 92.2%, 80.6% and 76% for renCR, renVGPR, renPR and renNR achieved by 24-months respectively; P<0.001). OS advantage for patients achieving renVGPR/CR over renPR/NR was maintained in a time-covariate multivariate analysis. eGFR progression was predictive for CI of RRT and OS and was inversely correlated with the depth of renal response.

Conclusions: New renal response criteria based on reduction in proteinuria are validated. These criteria highlight the importance of achieving a deep renal response to improve renal and overall survival. eGFR progression predicts progression to dialysis and death.



Abs C05

3. Treatment of MGCS

DARATUMUMAB BASED REGIMENS FOR THE THERAPY OF PATIENTS WITH MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE

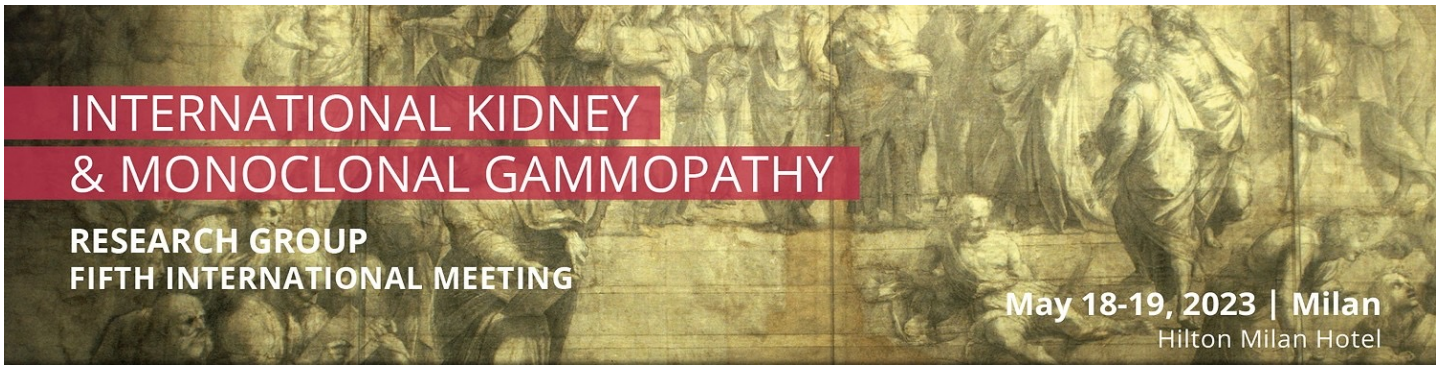
F. Theodorakakou[1], D. Fotiou[1], V. Spiliopoulou[1], P. Malandrakis[1], I. Ntanasis-stathopoulos[1], M. Migkou[1], M. Roussou[1], E. Eleutherakis-papaiakovou[1], E. Psimenou[1], C. Gakiopoulou[2], M. Gavriatopoulou[1], E. Terpos[1], M.a, Dimopoulos[1], E. Kastritis[1]

1. Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine
2. 1st Department of Pathology, National and Kapodistrian University of Athens

Introduction: Monoclonal gammopathy of renal significance (MGRS) encompasses a spectrum of renal pathologies with a causal link to an indolent plasma cell or B-cell clone, that requires anti-clonal treatment in order to salvage renal function. Therapies are borrowed from the field of myeloma and are similar to those used in AL amyloidosis, the most common among MGRS. Daratumumab (DARA), an antiCD38 monoclonal antibody, in combination with CyBorD, has been approved for newly diagnosed AL, however, data is still limited for other MGRS. We have previously reported our experience with DARA-based regimens in 25 patients (pts) with MGRS. In the current study we aim to provide further insights in a larger cohort with longer follow up.

Methods: This is a retrospective analysis that included 30 consecutive pts with MGRS, treated with DARA-based regimens in the Department of Clinical Therapeutics, Athens. The renal pathologies included 26 pts with MIDD (23 with LCDD), 2 with C3 nephropathy, 1 with PGNMID and 1 with cryo-crystaloglobulin nephropathy.

Results: The median age of the pts was 60 years and 70% were males; median baseline eGFR was 28.18 ml/min/1.73m2, 15 (50%) pts had baseline eGFR<30ml/min/1.73m2, and 3 (previously treated pts) were on dialysis at start of DARA. Median baseline proteinuria was 1.7gr/d (range 0.5 to 23). At start of therapy, 83% had hypertension requiring therapy. Median bone marrow infiltration was 11%, 19 (63%) pts had κ-light chain clones, median dFLC level was 92 mg/L, median serum M-peak was 0.2 gr/dl; 25 (83%) pts had measurable disease by standard criteria, and in 2 pts immunofixation was negative but the clone was detected using Next Generation Flow cytometry in the bone marrow. Seventeen pts received DARA as primary therapy, either with dexamethasone (n=4) or with bortezomib-based combinations (n=13), 11 received DARA with dexamethasone as second line therapy, 1 patient received DARA with lenalidomide and dexamethasone as third line and 1 received DARA and dexamethasone as fourth line. A median of 6 cycles of DARA was given. The overall hematologic response rate (ORR) was 77%, with CR in 7 (23%), VGPR in 8 (27%) and PR in 8 (27%) patients, per ISA criteria. Eleven pts (37%) had achieved hematologic response with dFLC<30mg/L (Milani et al, ISA 2022). The responses rates were similar for previously treated or previously untreated pts (76% and 77%); DARA in combination with bortezomib led to higher and deeper responses compared to DARA monotherapy (ORR: 87% vs 67% and CR/VGPR: 73% vs 27%). Responses were similar for pts with baseline eGFR<30 and ≥30ml/min/1.73m2 (73% and 79%). Fourteen pts were evaluable for MRD and among them 6 (43%) were MRDneg. The median follow-up of the cohort is 41.3 months. At 6 months, 18 (60%) pts had achieved a reduction of proteinuria by 30% and 9 (30%) had a reduction of proteinuria by 60%; 8 (27%) had improved their renal function by more than 25%, while 5 (17%) had a reduction of eGFR by at least 25%. One-, 2- and 3- year dialysis rate was 15%, 18% and 30%, respectively. The toxicity was manageable; infusion related reactions, occurred in only 2 pts and both were grade 1; 2 pts required hospitalization due to grade 3 infections.
Conclusions: The introduction of daratumumab in the therapeutic landscape of patients with MGRS is a safe and very effective option, that in combinations with bortezomib leads to high rates of hematologic responses and improvement in renal function.



Abs C06

2. Diagnosis of MGCS

A SUBSET OF PATIENTS WITH RENAL AL-AMYLOIDOSIS PRESENT WITHOUT SIGNIFICANT PROTEINURIA AND DISPLAY POOR RENAL OUTCOMES

N.senot (1), Jb.gibier (2), M.rabant (3), E.esteve (4), M.colombat (5), E.ferriere (6), K.dessaix (7), F.bridoux (8), C.cohen (6)

1 internal medicine department HEGP
2 Pathology department CHU de Lille
3 Pathology department Necker hospital
4 Nephrology department Tenon hospital
5 Pathology department Oncopole de Toulouse
6 Nephrology department Necker hospital
7 Nephrology department CHU
8 Nephrology department CHU de Poitiers

AL amyloidosis is a systemic disorder triggered by Congo-red positive tissue deposits of immunoglobulin light chains organized into ! sheets. Heart and kidney are the most frequently involved organs, and typical presentation of renal AL-amyloidosis consists of heavy albuminuria resulting in nephrotic syndrome. These features usually drive the indication for a kidney biopsy, unless the diagnosis has been secured by noninvasive biopsies. However, renal AL amyloidosis may sometimes feature predominant vascular deposition and present with lower degree of proteinuria, a situation where kidney biopsy is rarely considered. To date, the clinicopathological spectrum of renal AL amyloidosis without nephrotic-range proteinuria remains ill defined.

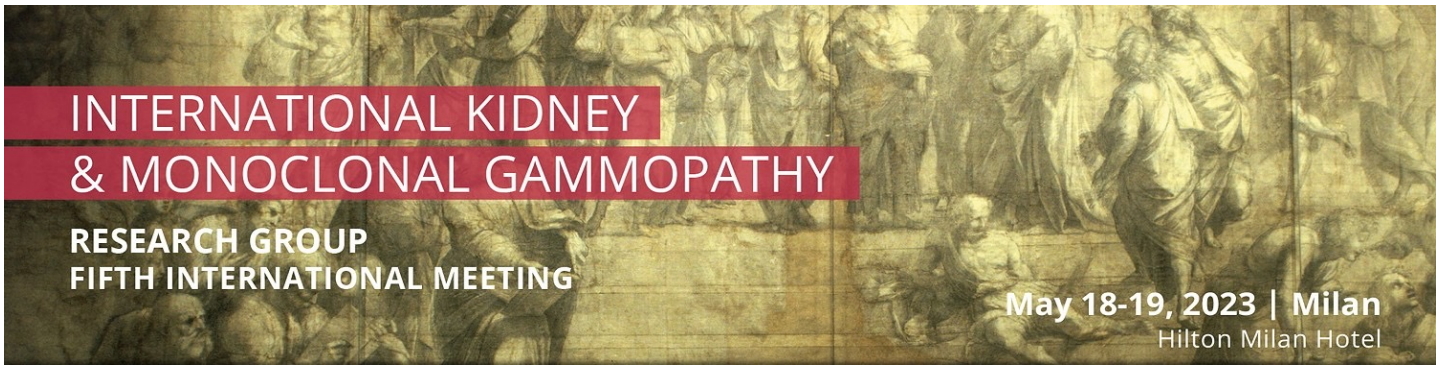
To better characterize the clinical, biological and pathological presentation and outcomes of patients with AL-amyloidosis and low-grade proteinuria, we performed a retrospective multicentric study in France. We collected data for 35 patients with kidney biopsy-proven AL-amyloidosis and proteinuria/creatininuria ratio < 1g/g at diagnosis. At diagnosis, median proteinuria was 0.58 g/g (0.37-1) with median serum creatinine level of 167 (127-213) µmol/L and median estimated glomerular filtration rate (eGFR) of 36.2 (24.3-49.6) ml/min/1,73 m2. Cardiac involvement was present in 67% of cases. According to Mayo 2004 staging, patients were classified as stage 1 (5%), stage 2 (28%) and stage 3 (61%).

Monoclonal gammopathy was detected thirty patients (93%). Hematological diagnosis was symptomatic multiple myeloma (n=5, 41%), Waldenström's macroglobulinemia (n=3, 9%) or MGCS (n=18, 56%).

Central review of 28 kidney biopsies revealed predominant vascular amyloid deposits in all cases, whereas 8 patients showed concurrent moderate glomerular involvement. Deposits were composed of kappa light chains in 12 cases, and lambda light chains in 16 patients. Interestingly, significant degree of interstitial fibrosis (median of 27.5% (15-36.25)) was observed, consistent with low baseline eGFR level.

Data on treatment modalities was available for 28 patients. Most patients (22/28 patients, 79%) received first-line triplet regimen combining dexamethasone, alkylating agent and bortezomib (n=14, 50%) or the melpahalan dexamethasone doublet (n=8, 29%). Hematological response rate was 43%, with CR and VGPR rates of 19% (n = 4) and 24% (n = 5), respectively. Renal response occurred in only 17% of patients. Median overall survival was 82 months and was dramatically affected by hematological response (HR), with median OS of 178 months in patients with VGPR/CR compared to 16 months in patients with NR/PR (p=0.002). Renal median survival was 56 months.

In conclusion, prominent renal vascular AL-amyloidosis is associated with severe initial presentation and poor outcomes. This is probably the consequence of late diagnosis due to poorly symptomatic disease in the absence of nephrotic-range proteinuria. We emphasize that kidney biopsy should be considered in patients with monoclonal gammopathy and otherwise unexplained kidney failure.



Abs C07

3. Treatment of MGCS

CHARACTERIZATION, OUTCOME AND IDENTIFICATION OF PROGNOSTIC FACTORS FOR PATIENTS WITH SYSTEMIC AL AMYLOIDOSIS REQUIRING DIALYSIS PRIOR TO INITIAL ANTI-CLONAL THERAPY

L. Sester1, P. Milani2, F. Theodorakakou3, C. Bellofiore2, M. Basset2, T. Dittrich1, J. Beimler4, F. Aus Dem Siepen5, D. Fotiou3, U. Hegenbart1, E. Kastritis3, G. Palladini2, S. Schönland1

1 Medical Department V and Amyloidosis Center, University Hospital,

2Amyloidosis Research and Treatment Center, Fondazione IRCCS Policlinico San Matteo, and the Department of Molecular Medicine, University of Pavia,

3 Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens,

4 Medical Department of Nephrology, Heidelberg University Hospital,

5 Medical Department of Cardiology, Heidelberg University Hospital

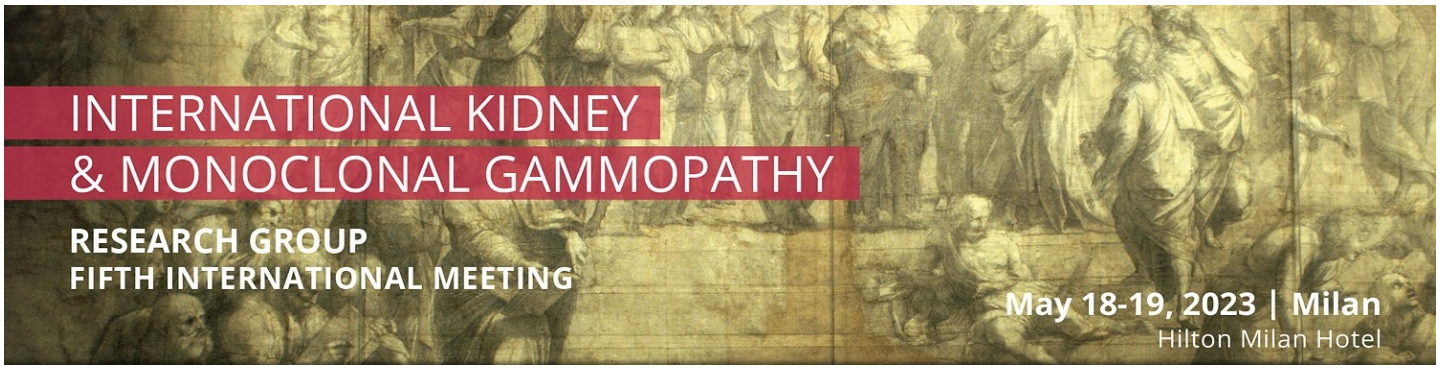
Introduction: AL amyloidosis is a rare disease leading to deposition of immunoglobulin light chains (LC) in various organs. These LCs are usually produced by a small plasma cell clone. Established therapy is directed against these B cell clones. The heart and kidneys are most often affected. Renal involvement leads to nephrotic syndrome and kidney failure. It occurs in up to 70% of patients (pts) with AL amyloidosis and results in significant morbidity and about 30% of affected pts require dialysis during the course of their disease. In a minority dialysis requirement occurs prior to initiation of therapy, but no detailed analysis of this group is yet available in the literature. There is an urgent need for criteria to assess prognosis and outcome in these pts.

Methods: We systematically searched the prospectively maintained databases of 3 amyloidosis centers for pts with biopsy-proven AL amyloidosis who received dialysis before initial therapy. All pts gave written informed consent. The study was approved by the institutional ethics committee.

Results: We identified 68 pts (Heidelberg: 32, Pavia: 24 and Athens: 12). Most pts were males (65%) and their median age was 65 years (range: 41-82 years). Most pts had lambda LC (71%) and a rather small and indolent B cell clone as underlying disease (51% MGCS (<10% PC), 40% SMM (>10% PC), 9% MM (CRAB pos.)). The median dFLC was 208 mg/l (range: 0-13999 mg/l). Kidneys were involved in 93%, followed by heart (57%) and soft tissue (29%). 41% of pts had involvement of >3 organs. The median value of residual urine output was 825 ml/day (range: 0-3020ml/day), while anuria occurred in 19% and oliguria in 28% of pts. Median proteinuria was 5628 mg/24hours (range: 250-26760) and median albuminuria was 1671 mg/24h (range: 8-13743). A bortezomib-based therapy was administered in 90% (53/58 pts) of those who received induction therapy. The overall survival (OS) and progression-free survival (PFS) rates did not significantly differ among the 3 centers: Median OS was 42.7 and PFS was 27.7 months (mo) (Figure 1c). The median follow-up was 62 mo and did was not significantly different among the 3 centers.

Figure 1a shows the results of univariate analysis for OS; pts with MGCS had a significantly better OS compared to those with SMM or MM. However, there was no significant difference based on the level of dFLC, number of involved organs, presence of anuria, serum creatinine or proteinuria levels. There was no significant difference based on NT-proBNP level; but pts with higher levels of hsTNT/TnI (Figure 1b) had a significantly worse OS. Response data were available for 49 pts at 3, 44 pts at 6, and 41 pts at 12 mo. Although OS did not differ statistically, pts who achieved >very good partial remission tended to have longer median OS (60.3, 94.5 and 60.3 mo at the 3, 6 and 12 mo landmarks) compared to those who did not (42.7, 42.7 and 42.1 mo at 3, 6 and 12 mo landmark, p=0.19, 0.079 and 0.15, respectively).

Conclusion: This multicenter study provides important insights into the characteristics and outcomes of pts with AL amyloidosis who require dialysis prior to initial therapy. The underlying clonal disease and markers of cardiac damage seem to be the most important prognostic factors. Such pts can have long OS despite need for dialysis but treatment strategies may need to be adapted to their special needs.



Abs P01

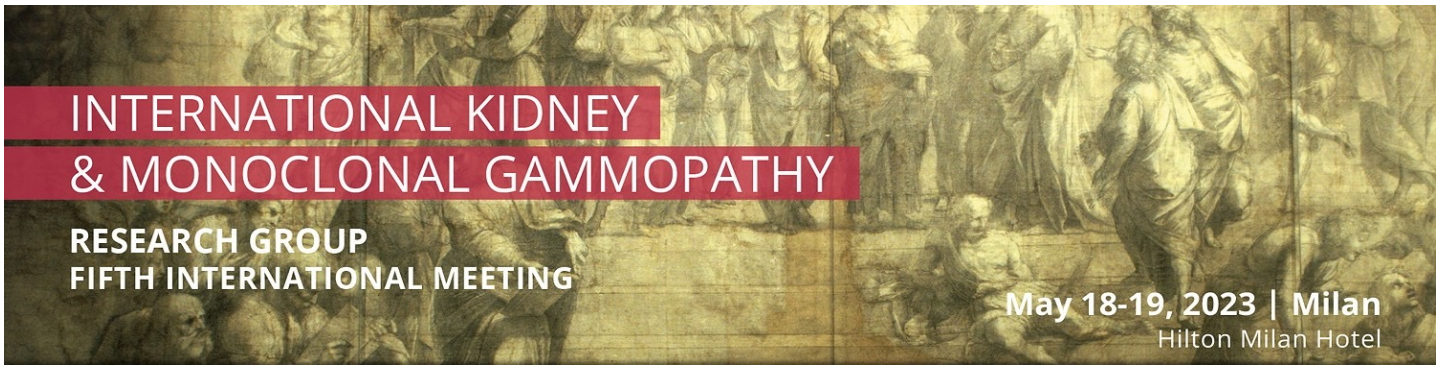
2. Diagnosis of MGCS

SCREENING FOR ALBUMINURIA IN PATIENTS WITH MONOCLONAL GAMMOPATHY OF UNCERTAIN SIGNIFICANCE: A SINGLE CENTRE EXPERIENCE

R. Rana, J. Pinney, P. Cockwell, M. Drayson, G. Pratt, R. Powell

Renal Department, Queen Elizabeth Hospital, University Hospitals Birmingham, UK
Haematology Department, Queen Elizabeth Hospital, University Hospitals Birmingham, UK
Institute of Immunology and Immunotherapy, University of Birmingham, UK

Albuminuria is biomarker of kidney damage and may be indicative of monoclonal gammopathy of renal significance (MGRS) in patients with a monoclonal gammopathy. Guidelines relating to screening for albuminuria in patients with monoclonal gammopathy of uncertain significance (MGUS) are not well defined and it is not known whether this should be a part of baseline assessment. This study evaluated 349 patients followed up in the nurse led telephone MGUS clinic. Patients were sent a questionnaire and screened for albuminuria with spot urine albumin creatinine ratio (ACR). Overall, 281/349 (81%) patients provided a urine sample. 70/281 (25%) had evidence of albuminuria (ACR >3 mg/mmol). Of the 70 patients, 54 (77%) had moderate albuminuria (ACR 3-30 mg/mmol) and 16 (23%) had heavy albuminuria (ACR > 30 mg/mmol). 24/70 (34%) patients were already under renal follow up. Defining the prevalence of albuminuria in this cohort resulted in a new diagnosis of AL amyloidosis in 1 patient and identified 45/281 (16%) patients that may benefit from a repeat ACR test and/or on-going renal opinion.



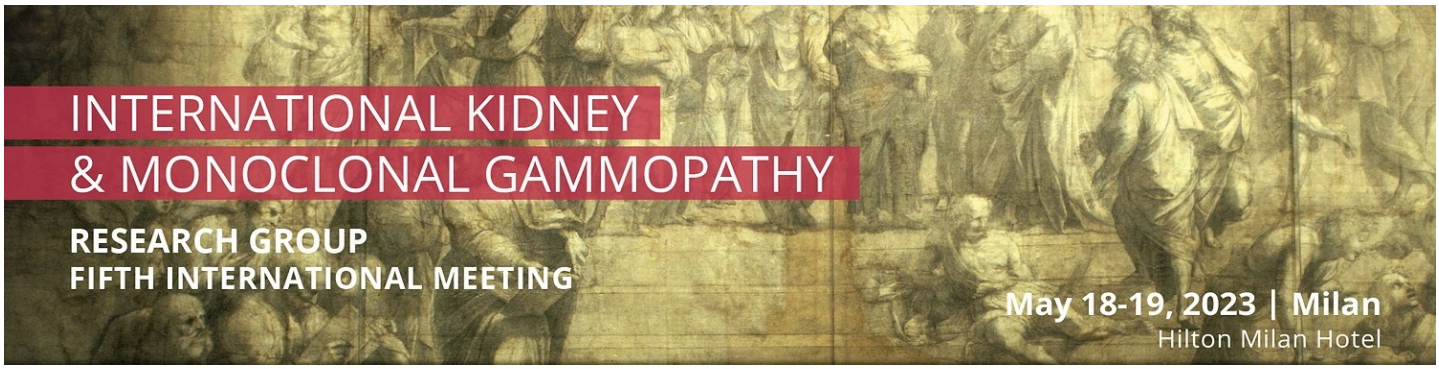
Abs P02

2. Diagnosis of MGCS

CLINICAL AND PATHOLOGICAL CHARACTERISTICS OF MGRS: A SINGLE-CENTER EXPERIENCE OVER TEN YEARS

C. Nie, H. Lee, K. Cheema, P. Duggan, S. Mcculloch, J. Tay, V. Jimenez-zepeda
Department of Medicine, University of Calgary

Background: Monoclonal gammopathy of renal significance (MGRS) is a heterogeneous and relatively recently defined disorder which encompasses many renal and hematologic pathologies. MGRS remains a rare disease and there is a need for more literature regarding its treatment and outcomes. In this study, we share our center's experience with MGRS including incidence of different renal pathologies, clone type, renal and hematological response to therapy, and progression-free survival.
Patients and methods: Data from 36 patients diagnosed with MGRS between 2013 and 2022 at a single Canadian tertiary care center were retrospectively analyzed. All cases required renal biopsy. Initial treatment included regimens containing bortezomib, rituximab, or cyclosporin, or steroids only. Parameters studied included incidence of different renal pathologies, clone type, depth of hematological response, renal survival (RS), overall survival (OS), and progression-free survival (PFS).
Results: Out of 36 patients, there were 10 cases of monoclonal immunoglobulin deposition disease, 8 of proliferative glomerulonephritis with immune deposits, 5 of microtubular immune deposits including immunotactoid and types 1 and 2 cryoglobulinemic nephropathy, 3 of C3 glomerulonephritis, 2 of renal HC amyloidosis, and 8 of other diagnoses. There were 21 cases with a plasma cell clone identified in bone marrow, 2 each of B cell and low-grade lymphoma, one atypical T cell clone, and 10 cases without an expanded clone on bone marrow biopsy. In terms of renal survival, 6 out of 36 patients required renal replacement therapy (RRT), and time from diagnosis to RRT varied from 3.4 to 59.3 months (median 7.8). A total of 4 patients died; median progression-free survival was 59.3 months. Very good partial hematological response or better was associated with renal response.
Conclusion: Our experience confirms that MGRS is a heterogeneous disease and adds to the literature concerning the diagnosis and treatment of MGRS. Successful treatment of the underlying hematological disorder with targeted therapy is more likely to lead to an improvement in renal function.



Abs P03

2. Diagnosis of MGCS

DIAGNOSIS AND SUBTYPING OF CARDIAC AMYLOIDOSIS BY THIOFLAVIN-T STAINING AND IMMUNO-LABELING TECHNIQUES

S. Wang[1], S.x. Wang[1].

Laboratory of Electron Microscopy, Pathological Center, Peking University First Hospital.

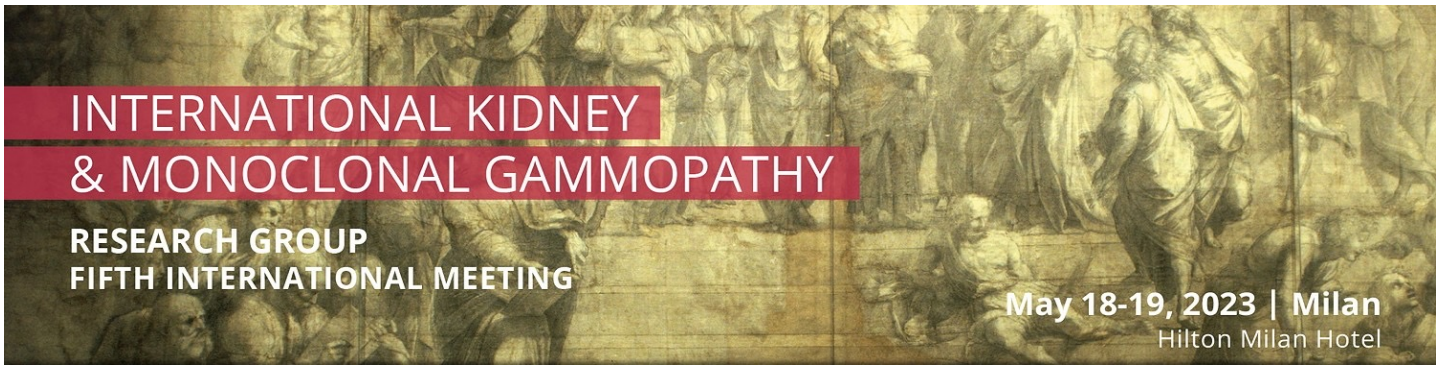
Introduction: Amyloid light chain (AL) amyloidosis, characterized by the fibrillar deposits derived from monoclonal immunoglobulin (Mlg) light chain in the extracellular space, is the most common type of monoclonal gammopathy of clinical significance (MGCS). The heart is frequently affected by AL and transthyretin (TTR) amyloidosis, which are conducted with different therapies and undergoing different long-term outcomes. Thus, the early diagnosis and subtyping of cardiac amyloidosis is very important. Endomyocardial biopsy is proposed to be the gold criteria in diagnosing cardiac amyloidosis by identifying the Congo red-positive deposits with green-yellow birefringence under polarized light. Except for Congo red (CR), Thioflavin-T (ThT) was demonstrated to be a potent fluorescent marker for detecting amyloid, and subtyping of amyloidosis can be determined by immuno-labeling techniques such as immunofluorescence (IF) and immune-electron microscopy (IEM). In this study, we explore the sensitivity and specificity of ThT staining for amyloid diagnosis, and of immuno-labeling techniques for amyloid subtyping in endomyocardial biopsies.

Methods: Forty endomyocardial biopsy specimens suspected of amyloidosis received in Pathological Center of Peking University First Hospital from 2021 to 2022 were enrolled in this study. The specimens were examined by light microscopy (hematoxylin and eosin stain, CR), IF (detection for κ/λ light chain and TTR) and transmission electron microscopy. IEM (labeling for κ/λ light chain and TTR) were used to further confirm the subtypes on all cases. ThT staining was performed on fresh frozen tissue and viewed under fluorescent microscope. The extent of amyloid deposition was evaluated semi-quantitatively, both for CR and ThT staining: grade 0 (negative, no amyloid detectable); grade 1 (<25% of the tissue was involved); grade 2 (25~50% of the tissue was involved); grade 3 (>50% of the tissue was involved).

Results: 32 of 40 cases were diagnosed as cardiac amyloidosis and the other eight cases were non-amyloid cases as negative controls. Amyloid deposits in frozen sections of endomyocardial biopsies were strongly stained with ThT revealing as green fluorescence when excited at 490nm. ThT staining was positive in 29/32 cases (sensitivity 91%), CR staining was positive in 31 cases (sensitivity 97%). For the eight negative control cases, the ThT staining was negative in all 8/8 (specificity 100%) and CR staining was negative in seven cases (specificity 88%). The grade of CR and ThT staining was evaluated independently and both methods correlated strongly in all 40 cases (Spearman r=0.69, p<0.001).

For the 32 cardiac specimens, the amyloid was successfully subtyped by IF in 25 cases (sensitivity 78%). Apart from one case classified as AL-λ by IF, the other cases were subtyped by IEM definitely (31/32, 97%). When combined use of IF and IEM, the diagnostic classification was increased to 100% in cardiac amyloidosis.

Conclusion: ThT staining showed high sensitivity (91%) and a supreme specificity (100%) in diagnosing cardiac amyloidosis, and can be promisingly applied for clinical diagnosis of cardiac amyloidosis in frozen tissues. Amyloid deposits can be reliably subtyped in cardiac specimens by immuno-labeling techniques, especially IEM, the success rate of classification on amyloid can reach to 100% when IF and IEM were combined.



Abs P04

2. Diagnosis of MGCS

DE NOVO MGRS/LCDD IN A KIDNEY ALLOGRAFT

A Ali

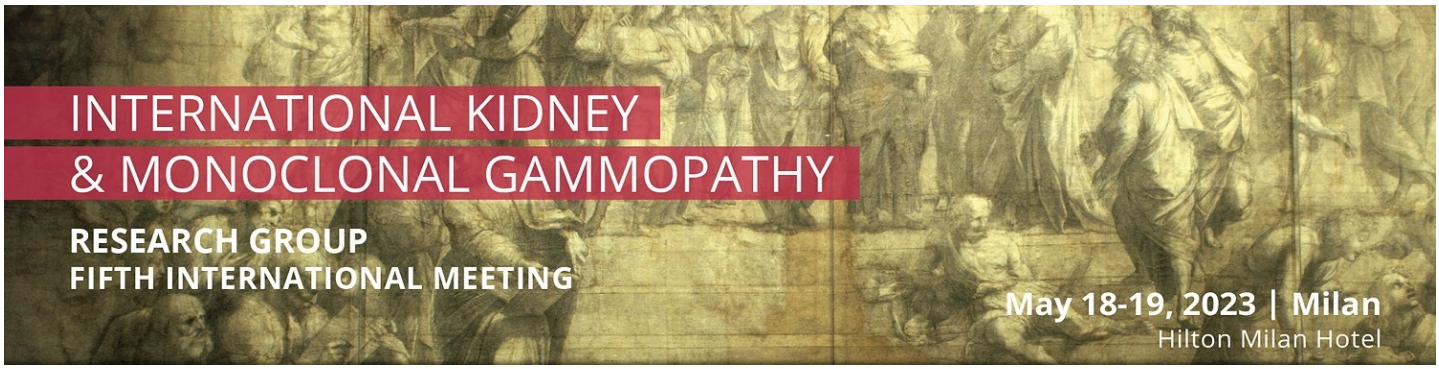
Nephrology and Renal Transplantation Centre, The Medical City

Monoclonal gammopathy of renal significance (MGRS) identifies patients with B cells clone who do not meet the criteria of multiple myeloma or lymphoma but cause significant renal disease. Light chain deposition disease (LCDD) is a histopathological pattern of MGRS characterized by the deposition of specific monoclonal light chains in the kidneys and other organs. Despite the scarcity of clinical trials, it is known that recurrence is the usual outcome in all MGRS-associated lesions after a kidney transplant with poor graft survival. The absence of unified management guidelines even complicates this. Furthermore, de novo LCDD is very rare in kidney transplant recipients.

Here we present a 50 years old lady, three years after a live unrelated donor kidney transplant, who presented with rapidly progressive glomerulonephritis and dialysis requiring acute kidney injury (AKI). Her primary ESKD was due to stone disease and hypertension, but she had no history of proteinuria. She had a history of new-onset DM after the transplant with no evidence of retinopathy. Her urine exam revealed active urinary sediments, hematuria, and proteinuria. Kidney allograft biopsy was consistent with crescentic GN and kappa light chain deposits on IF with no evidence of rejection nor myeloma on bone marrow study.

A bortezomib-based therapy was initiated, and she remained dialysis-dependent for three months. Five years after treatment, her serum creatinine is 1.9 mg/dl, with no evidence of plasma cells on bone marrow, still positive urine testing for the light chain, but at a normal free light chain ratio.

The present case highlights the possible occurrence of de novo LCDD in kidney transplants, with its organ-threatening presentation. Therefore, early detection and initiation of bortezomib-based therapy could save the graft and the patient.



Abs P05

3. Treatment of MGCS

IMPACT OF AUTOLOGOUS STEM CELL TRASPLANTATION IN LIGHT CHAIN AMYLOIDOSIS WITH RENAL INVOLVEMENT. EXPERIENCE IN A SINGLE TERTIARY HOSPITAL

E. Alejo[1], B. Puertas[1], C. Agulló[2], B. Rey[1], M. Heras[3], A. Tyszkiewicz[3], F. Escalante[4], A. Bárez[5], A. García-mateo[6], Fj. Díaz-gálvez[7], Jm. Alonso[8], R. Hernández[9], A. García De Coca[10], R. López[11], A. Navarro[1], L. López-corral[1], N. Puig[1], Mv Mateos[1], V. González-calle[1]

1 Hematology department, University Hospital of Salamanca, CIBERONC; 2 Biochemistry department, University Hospital of Salamanca; 3Nephrology department, University Hospital of Salamanca; 4 Hematology department, Hospital of León; 5 Hematology department, Hospital of Ávila; 6 Hematology department, Hospital of Segovia; 7 Hematology department, Hospital of Burgos; 8 Hematology department, Hospital of Palencia; 9 Hematology department, Hospital of Zamora; 10 Hematology department, Clinical Hospital of Valladolid; 11 Hematology department, Hospital of Plasencia

Background

AL amyloidosis is a clonal plasma cell (PC) disorder characterized by deposition of amyloid fibrils leading to organ disfunction. Cardiac and renal involvement are the most frequent. The addition of daratumumab to the first line treatment bortezomib-cyclophosphamide-dexametasone (CyBorDex) is challenging the role of autologous stem cell transplantation (ASCT), and ASCT can be deferred when hematologic complete response (hemCR) is achieved.

Aims

To describe the baseline characteristics of AL amyloidosis patients with renal impairment undergoing ASCT. To analyze the effect of ASCT in improving hematologic responses (HR) and renal responses (RR) at day +100 and in terms of progression free survival (PFS) and overall survival (OS).

Methods

An observational retrospective study was designed including patients who underwent ASCT between 1999 and 2022 at the University Hospital of Salamanca. Patients were classified according to the staging system for risk of progression to end-stage renal failure developed by Palladini et al. HR were assessed according to the International Society of Amyloidosis criteria and RR according to graduate response criteria established by Muchtar *et al.*

Results

From our total series of 55 patients with renal involvement, 22 (40%) underwent ASCT, with a median age of 54.5 years (40-70). Median of damaged organs was 2 (1-4), >10% PC at diagnosis were found in 27.3% and 35.3% had t(11;14). Eight were classified into renal-stage I; 13, stage II and 1, stage III.

Induction was administered in 16 (72.7%), with CyBorDex being the most regimen used, and 6 underwent directly to ASCT. Melphalan 200 mg/m2 was the preferred conditioning regimen (77.3%) while the others received Melphalan 140 mg/m2. None were on dialysis, but half had nephrotic range proteinuria at ASCT.

At day +100 evaluation, 19 had evaluable disease, the remaining 3 died within the first three months: 2 from septic shock and 1 from progression (*Table 1*). Seven (36.8%) achieved hemCR at +100 (5 maintained the response achieved preASCT and 2 prior very good partial response (VGPR) upgraded it to CR); 5 (26.3%), VGPR; and 14 (73.7%) achieved RR (50% already were in RR preASCT).

Among the 5 patients in hemCR prior to ASCT, the response at +100 was maintained in all of them. High-tumor burden disease at diagnosis (>10% PC) was found in 2. Only 1 relapsed, 44 months after ASCT.

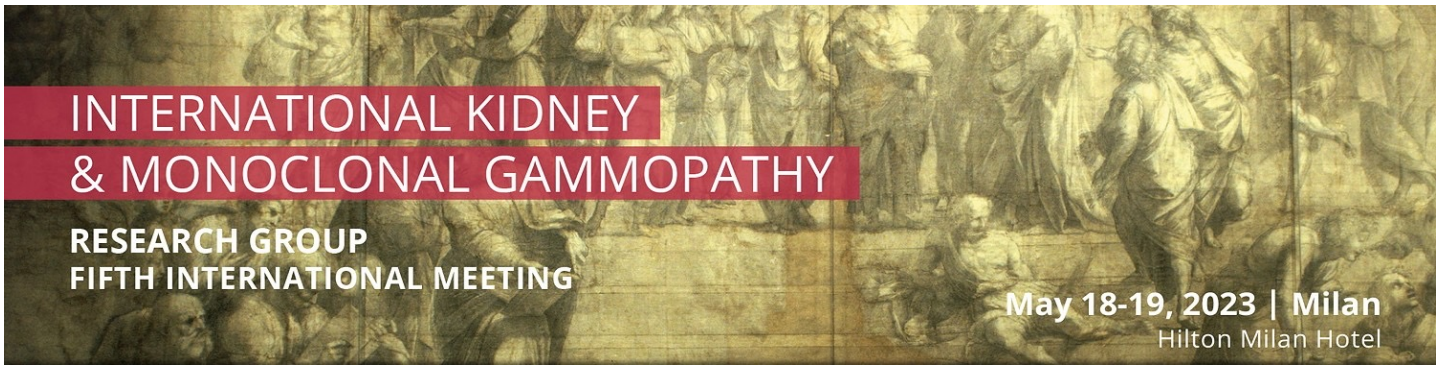
With a median follow-up of 74.3 months (3.3-154.2), median PFS and OS from ASCT was 33.9 (0.17-148.2) and 74.2 months (0.17-154.2), respectively. PFS in patients with exclusive renal involvement was longer than in those with 2 or more involved organs (not reached vs 28.3 months; p=0.06). Nephrotic range proteinuria at ASCT did not impact on outcomes.

Conclusion

1)A total of 40% of patients with AL amyloidosis with renal involvement underwent ASCT in our center, highlighting that a careful selection was made, resulting in low early mortality.

2)More than 60% achieved at least VGPR at day +100, which is the optimal response after ASCT nowadays, and 70% achieved RR. Among those receiving induction, ASCT improved HR to VGRP or better in nearly to 30% and RR in 20%. All patients in hemCR at ASCT held up the response at +100, and nearly half of them would have undergone ASCT nowadays due to high-tumor burden disease at diagnosis.

3)Results about PFS and OS from ASCT were consistent with other series, with 84%, 55% and 20% of patients alive at 5, 10 and 15 years, respectively.



Abs P06

3. Treatment of MGCS

MANAGEMENT OF ACUTE KIDNEY INJURY IN FRAIL PATIENTS WITH BIOPSY-PROVEN CAST NEPHROPATHY: A COMBINED APPROACH WITH CHEMOTHERAPY PLUS SUPRA-HEMODIAFILTRATION WITH POST-ADSORPTION ENDOGENOUS REINFUSION

R. Fenoglio1, M. Cozzi1, E. De Simone1, S. Sciascia1, D. Roccatello1

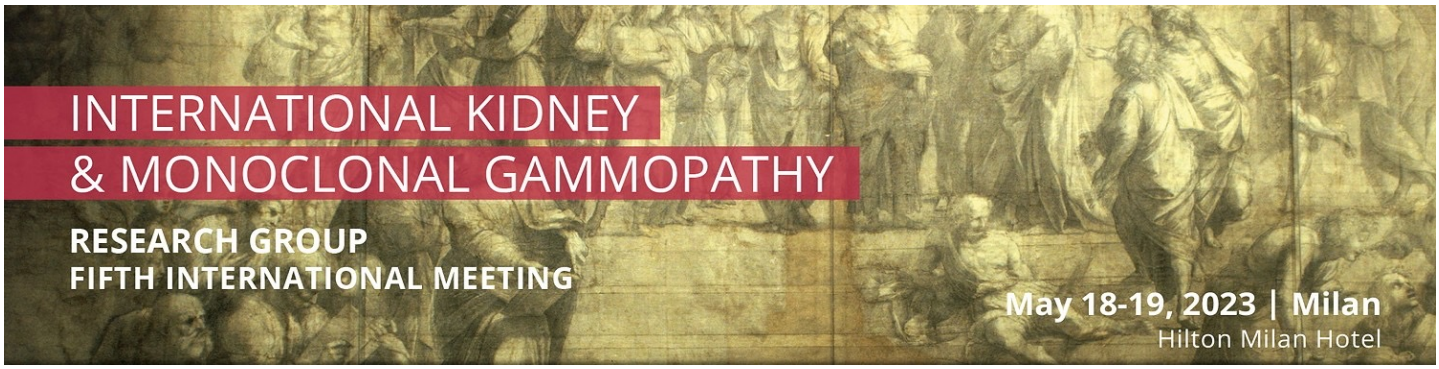
1 University Center of Excellence on Nephrologic, Rheumatologic and Rare Diseases (ERK-net Member), Department of Clinical and Biological Sciences, San Giovanni Bosco Hub Hospital, University of Turin, Italy.

Background Patients with multiple myeloma (MM) often have kidney involvement with acute kidney injury (AKI) and the need of renal replacement therapy (RRT), frequently due to cast nephropathy (CN). Hemodiafiltration with endogenous reinfusion (HFR)-Supra technique allows effective removal from the circulation of free light chains (FLCs), responsible for tubular damage, and may favor short-term recovery of kidney function.

Methods We performed a retrospective observational study on patients with MM with AKI stage III in need of RRT, who received HFR-Supra treatment plus standard of care chemotherapy between 2014 and 2021. The following parameters were considered: FLCs subtype, FLCs levels at presentation and at the end of HFR-Supra therapy, reduction rate of FLCs after HFR-Supra therapy, serum creatinine (SCr) at presentation, renal outcome at 3 months of follow up.

Results 19 patients affected by MM (58% λand 42% k chain), including 16 with biopsy-proven CN, received HFR-Supra therapy plus chemotherapy. Median FLCs levels at diagnosis were 7984 mg/l for λchains and 9078 mg/l for k chains. Mean SCr at presentation was 8,8 mg/dl. HFR-Supra were performed on a daily base. Mean number of sessions was 9 (±2) per patient. At the end of HFR-Supra median FLCs levels were 2275 mg/l for λchains, 2050 mg/l for k chains, with a median reduction of 63% for λchains and 68% for k chains. At 3-month follow up 6 patients (31,6%) had discontinued dialysis with partial or complete recovery of kidney function (mean SCr 1.6mg/dl).

Conclusions: The synergistic effect of HFR-Supra with chemotherapy allowed dialysis discontinuation in one third of patients who presented with MM and AKI stage III in need of RRT. In our experience, HFR-Supra represents a relatively low cost and effective adjunctive therapy for these patients.



Abs P07

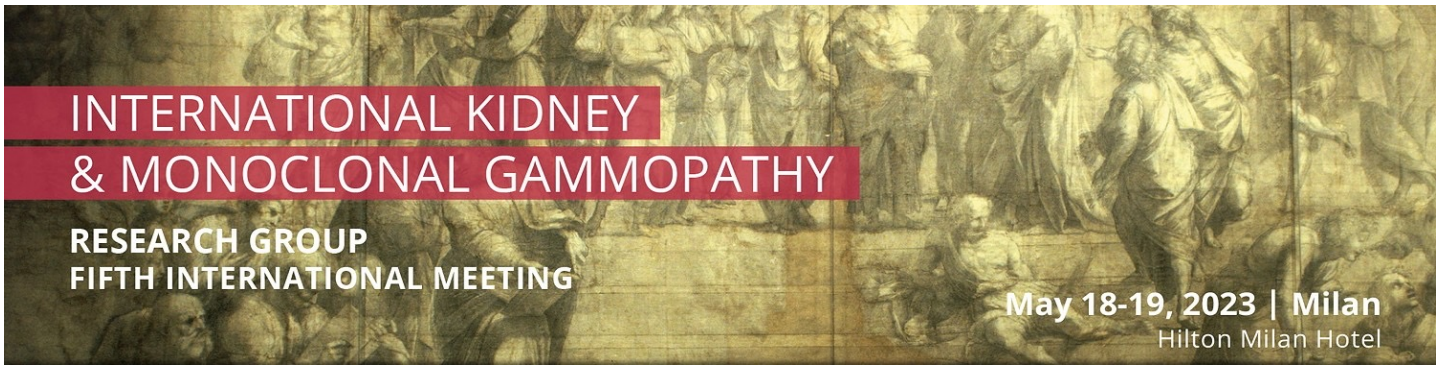
3. Treatment of MGCS

DARATUMUMAB MONOTHERAPY IN SEVERE PATIENTS WITH AL AMYLOIDOSIS AND BIOPSY-PROVEN RENAL INVOLVEMENT

Roberta Fenoglio1, Gianluca Rabajoli1, Andrea Careddu1, Simone Baldovino1, Savino Sciascia1, Dario Roccatello1.

1University Center of Excellence on Nephrologic, Rheumatologic and Rare Diseases (ERK-net Member), Department of Clinical and Biological Sciences, San Giovanni Bosco Hub Hospital, University of Turin, Italy.

Background and Aims: Daratumumab is an anti-CD38 monoclonal antibody recently approved as a first-line therapy on top of standard therapy for the treatment of multiple myeloma and AL amyloidosis. The following data describe the good results reported by our group and the long-term experience achieved in recent years on the efficacy of daratumumab used in monotherapy. Methods: This paper describes 17 patients (pts) treated with Daratumumab alone, 24 iv administration at a dose of 16 mg/kg. All of them had an histological confirmation and staging of renal involvement before treatment was started and were ineligible for ASCT. A bone marrow biopsy excluded overt multiple myeloma and the patient could either be naïve or refractory. Haematological and organ response was evaluated every 4 infusions. Responses were defined by using the International Society of Amyloidosis extended criteria. When feasible, the patient who underwent the whole cycle of therapy underwent a second kidney biopsy at the end of the treatment. Results: The mean age at diagnosis was 73 years. 16/17 patients had proteinuria that was associated with renal function impairment in 11. Two patients were on dialysis at the time of therapy initiation. 9 pts completed the treatment; 13 over 17 underwent at least 12 infusions. At this time, At the 12th administrations 11/13 pts (84,6%) had an overall hematological response. 6 pts (46,5%) achieved a complete hematological response, 5 pts had a very good partial response (38%), and 2 were non responders (15,5%). As regard to renal response 5/13 had already achieved an organ response; 6 didn't meet renal response criteria yet; the 2 pts who were in dialysis at the time of therapy initiation, remained on dialysis. 1 of them had a complete hematological and cardiac responses, the remaining pt didn't have any response. 7/9 achieved a renal response; the 2 remaining pts who were in dialysis at the time of therapy initiation, remained on dialysis. A significant decrease in 24-hour proteinuria from 6,02 hours to 1,28 g/die ($p < 0.005$) with stabilization or improvement of sCr ($p=0.17$) were observed. 8/9 pts with cardiac involvement obtained at least amelioration. At the end of follow-up (mean 30 months) 5 pts have persistent hematological and renal response. 1 pt with initial partial response had a relapse and initiated a treatment with Bortezomib plus cyclophosphamide and dexamethasone. Two pts died to COVID infection and cardiovascular disease respectively. The last pt is still alive and is currently being treated with a second line of therapy, because no hematologic or organ response was achieved with Daratumumab. 7 pts underwent a second kidney biopsy at the end of the treatment. Histological findings showed stable deposits in 6 over 7 cases, while the last one showed a reduction in the extention and amount of amyloid deposits. Conclusion The optimal management of pts with AL amyloidosis remains to be defined. Recently daratumumab has emerged as an appealing therapeutic alternative as shown by several reports. However, in clinical trials daratumumab was always added to bortezomib, cyclophosphamide and dexamethasone. Our data, based on the real life experience of our center, suggest that daratumumab monotherapy may represent an effective therapeutic option, capable not only of inducing a substantial improvement in the renal status in pretreated or naïve pts, but also of limiting progression of amyloid deposition.



Abs P08

4. Multiple myeloma and light chain cast nephropathy

ALBUMINURIA AT BASELINE AND 12-MONTHS IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA; RESULTS FROM THE UK NCRI MYELOMA XI TRIAL.

R. Rana, P. Cockwell, M. Drayson, G. Pratt, D. Cairns, C. Pawlyn, G. Jackson, F. Davies, G. Morgan, J. Pinney

Department of Renal Medicine, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK
Department of Haematology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
Clinical Trials Unit, University of Leeds, Leeds, UK
The Institute of Cancer Research, London, UK
Department of Haematology, University of Newcastle, Newcastle-upon-Tyne, UK
NYU Langone Health, 522 First Avenue, New York City, NY, USA

Kidney disease in myeloma is heterogenous and associated with worse outcomes. Albuminuria is a powerful adverse determinant of outcomes in kidney disease but there are limited data on patients with multiple myeloma. This study therefore evaluated the Myeloma XI trial at diagnosis and one-year for (i) albuminuria incidence and prevalence by urinary albumin creatinine ratio (ACR); and (ii) the relationship between ACR and excretory kidney function as categorised by estimated glomerular filtration (eGFR). Patients were matched for age, sex, baseline free light chain level and 12-month clonal response and 529 patients met the criteria. At presentation 305 patients (58%) had albuminuria (ACR >3 mg/mmol). In 15 patients (3%) this approximated to ≥1 gram/24 hours (ACR ≥70 mg/mmol). Albuminuria at baseline was not independently associated with a lower eGFR category at 12 months. At 12 months 162 patients (30%) had albuminuria. Further studies are needed to identify the impact of persistent albuminuria on long-term outcomes.