RESEARCH ARTICLE

Assessment of renal outcome following therapy in monoclonal immunoglobulin deposition disease: Emphasizing the need for a consensus approach

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Abstract

Monoclonal immunoglobulin deposition disease (MIDD), often associated with plasma cell dyscrasias, predominantly affects the kidneys. In this disease, hematologic response (HR) to treatment can be reliably assessed by International Myeloma Working Group (IMWG) consensus criteria, while uniform criteria for assessing renal response are lacking. We report a retrospective analysis of renal outcomes among 34 patients with MIDD. With most patients treated with bortezomib and autologous stem cell transplantation, 26 of 28 (94%) achieved very good partial HR or better. We demonstrate that both IMWG (based on estimated glomerular filtration rate, eGFR) and amyloid (based on proteinuria) criteria are needed to capture renal response: among 28 evaluable patients, 6 (21%) had isolated proteinuria, while 13 (46%) had isolated decreased eGFR. Using both criteria, which were concordant in patients with both decreased eGFR and proteinuria, 22 of 28 patients (79%) achieved a renal response, including 2 of 7 discontinuing dialyses. All 6 patients (100%) with isolated proteinuria and 7 of 13 (54%) with isolated decreased eGFR achieved renal response, suggesting that isolated proteinuria is an early manifestation of MIDD associated with reversible renal damage. Baseline eGFR predicted renal response ($p = .02$ by quartile) and survival ($p = .02$), while HR (CR vs. non-CR) did not, probably because of high HR rate. With a median follow-up of 110 months, the median overall survival was 136 months (95% CI: 79–NR) and median renal survival had not been reached. Prospective studies using uniform renal response criteria are needed to optimize the management of MIDD.

1 | INTRODUCTION

Randall-type monoclonal immunoglobulin deposition disease (MIDD) is one of the most common entities among monoclonal gammopathy of renal significance (MGRS), a recently named group of renal diseases that have in common the presence of an underlying nephrotoxic monoclonal immunoglobulin protein.[1–4] While the precise pathologic mechanisms that lead to the various distinct phenotypes involved in MGRS are diverse and generally poorly understood, characteristics used in the current classification system include the distinct

pathologic appearances on light microscopy, electron microscopy, and immunofluorescence, as well as the characteristic deposition sites within the kidney. In addition, distinctive clinical features allow for differentiation of the various phenotypes.

MIDD is typically associated with plasma-cell and lymphoid neoplasms. Its characteristic organ dysfunction is caused by the deposition of pathogenic monoclonal light and/or heavy chain immunoglobulin, most commonly in basement membranes of the kidneys, but also other organs such as lung or liver.[5–12] The monoclonal gammopathy may consist of light chains, heavy chains, or both, leading to the designations of light chain deposition disease (LCDD), heavy chain deposition disease (HCDD), or light and heavy chain deposition disease (LHCDD), respectively. Monoclonal protein deposits are visualized through light microscopy as non-organized globular structures and identified by immunofluorescence staining as immunoglobulin proteins. The ultrastructure involves electron-dense, nonfibrillar deposits visible in basement membranes by electron microscopy. Most LCDD cases are associated with kappa light-chain isotype,[7,12] and there is a known association with the V_k IV variability subgroup of human monoclonal kappa light chains.

Evidence-based guidelines on the management of MIDD (and MGRS in general) are lacking, and prospective trials have not been conducted. However, since this condition is often associated with an underlying plasma cell dyscrasia, patients have typically been treated with regimens used in multiple myeloma. Data from retrospective cohort series of patients with MIDD treated with these anti-myeloma regimens guide the clinical management of MIDD.[7–9,11,12] Several groups have reported on the efficacy of bortezomib,[9,13–16] autologous stem cell transplantation (ASCT),[9,17–22] and newer drugs such as daratumumab.[23] However, while hematologic responses (HRs) are well characterized based on the extensively vetted and adopted International Myeloma Working Group (IMWG) HR criteria,[24,25] uniform criteria for assessing renal response to treatment of the underlying hematologic condition are not well defined in patients with MIDD, and there is no standard of care. As a result, the assessment of renal function outcomes, the hallmark of MIDD, is not uniformly analyzed in published series. Here, we report our experience of treatment outcomes, particularly organ outcomes, in a retrospective cohort study of 34 patients with MIDD at two centers.

2 | METHODS

2.1 | Patients

We performed an institutional review board (IRB)-approved electronic query of pathology records at Memorial Sloan Kettering Cancer Center (MSK) and New York Presbyterian Hospital/Weill Cornell Medical Center (NYP-Cornell) to identify patients with a biopsy-proven diagnosis of MIDD. Patients were eligible for inclusion in this analysis if they received treatment and were subsequently followed at either institution. The demographics of eligible patients, including age, gender, and race, were collected from medical records. We also identified hematologic characteristics, including monoclonal immunoglobulin

isotype; levels of free light chain (FLC) by FLC assay; levels of serum monoclonal spike by serum protein electrophoresis (SPEP); levels of serum albumin; β2 microglobulin with corresponding staging according to the multiple myeloma International Staging System (ISS); and percentage of bone marrow plasmacytosis as determined by manual cell count of bone marrow aspiration and biopsy before treatment.

Renal characteristics identified included renal function and 24-hour proteinuria. Renal function was assessed by serum creatinine level and estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. Nephrotic-range proteinuria was defined as urine protein ≥3 g/24 h; and hematuria defined as >5 red blood cells/high power field. Treatment characteristics assessed included the induction therapy and combination regimens used, specifically whether bortezomib, lenalidomide, cyclophosphamide and ASCT were used in first-line therapy.

2.2 | Renal pathology

Renal biopsies from both institutions were processed according to standard methods and evaluated by light microscopy, immunofluorescence, and electron microscopy at NYPH-Cornell. We extracted renal pathologic data from available pathology reports and a renal pathologist (S.P.S.) reviewed the data for accuracy and confirmation of the diagnosis of MIDD, detailing the following: number of glomeruli; presence or absence of cortex or medulla in the biopsy; presence or absence and percent involvement of global glomerulosclerosis, focal segmental glomerulosclerosis, interstitial fibrosis, and tubular atrophy; grade of arteriosclerosis of renal arteries and arterioles; immunofluorescence staining graded 0 to 3+ for heavy chains (IgG, IgA, IgM) and light chains (kappa and lambda); degree of foot process effacement (percent); confirmation of glomerular and/or tubulointerstitial MIDD; and presence of other non-MIDD renal pathologic findings in the biopsy. Details of the pathologic data are not presented in this paper.

2.3 | Hematologic and renal response evaluation

We assessed HRs according to the IMWG uniform response criteria.[24,25] Renal responses were assessed on the basis of changes in both eGFR and proteinuria because of patients' diverse disease presentations; although most present with decreased eGFR along with variable degrees of proteinuria, some present with proteinuria and preserved eGFR while others with decreased eGFR without proteinuria. Therefore, the response criteria used were either (i) the IMWG renal response criteria or (ii) amyloid response criteria, respectively, for patients with decreased eGFR <50 ml/min/1.73 m^2 with or without significant proteinuria (>1 g/24 h), or patients with significant proteinuria (UTP >1 g/24 h) with or without preserved eGFR (>50 ml/min/1.73 m^2) at presentation. IMWG renal response criteria include the following: complete response (Renal CR), if eGFR <50 ml/min/1.73 m^2 prior to treatment improves to eGFR ≥60 ml/min/1.73 m^2; partial

TABLE 1 Baseline characteristics (N = 34)

Age (median, IQR)	49.5 (44–59)
Sex, n (%)	
Male	20 (59)
Female	14 (41)
Race, n (%)	
White	28 (82)
African American	6 (18)
Hypertension, n (%)	23 (68)
Hematologic characteristics	
Involved serum free light chain isotype, n (%)	
Kappa	31 (91)
Lambda	2 (6)
Kappa & Lambda	1 (3)
MIDD subtype, n (%)	
HCDD	2 (6)
LCDD	31 (91)
LHCDD	1 (3)
Involved FLC level, mg/dL (median, IQR)	129.3 (31.9–291)
Involved/Uninvolved free light chain ratio (median, IQR)	69.28 (14.2–206.1)
Serum M-protein, g/dL (median, IQR)	0 (0–0.3)
Bone marrow plasmacytosis, % (median, IQR)	20 (12.75–30)
Patients with bone marrow plasmacytosis ≧10%, n (%)	26 (77)
Serum albumin, g/dL (median, IQR)	3.95 (3.5–4.2)
β2 microglobulin, mg/L (median, IQR)	5.6 (4.5–8.65)
ISS stage, n (%)	
I	5 (15)
II	9 (26)
II	15 (44)
Not available	5 (15)
Lactate dehydrogenase, U/L (median, IQR)	196 (168–216)
Associated hematologic diagnosis, n (%)	
Multiple myeloma meeting IMWG criteria aside from eGFR	25 (74)
Smoldering myeloma	3 (9)
MGUS	4 (12)
Chronic lymphocytic leukemia	1 (3)
Waldenstrom macroglobulinemia + plasma cell dyscrasia	1 (3)
Patients meeting 2014 IMWG Revised Myeloma Defining Criteria excluding renal criterion, n (%)	
Hypercalcemia[a]	1 (3)
Anemia with hemoglobin <10 g/dL	15 (44)
Anemia with hemoglobin 2 g/dL below normal range[b]	3 (9)
Osteolytic bone lesions on imaging	11 (32)
Involved/Uninvolved serum FLC ratio > 100	12 (35)
Clonal bone marrow plasmacytosis ≥60%	3 (9)
Patients with ≥1 IMWG criteria for MM (excluding renal criterion)	25 (74)
Renal characteristics	
Estimated GFR (eGFR) by CKD-EPI prior to treatment (median, IQR)	23.2 (10.9–42.1)
Dialysis prior to treatment, *n (%)*	7 (21)

(Continues)

TABLE 1 (Continued)

24-h urine protein, mg/24 h (median, IQR)	2700 (525.15–5840)
Nephrotic-range proteinuria (≥3 g urine protein/24 h), n (%)	15 (44)
Hematuria at diagnosis, n (%)	5 (15)
Treatment characteristics	
Bortezomib-based therapy, n (%)	19 (56)
Lenalidomide-based therapy, n (%)	7 (21)
Cyclophosphamide, n (%)	8 (26)
Dexamethasone alone	5(15)
Melphalan + ASCT, n (%)	23 (68)

Abbreviations: CDK-EPI, Chronic Kidney Disease Epidemiology Collaboration; FLC, free light chain; HCDD, heavy chain deposition disease; IQR, interquartile range; LCDD, light chain deposition disease; LHCDD, light and/or heavy chain deposition disease; MIDD; monoclonal immunoglobulin deposition disease; ISS, International Staging System; MGUS, monoclonal gammopathy of undetermined significance; MGRS, monoclonal gammopathy of renal significance.
[a]Serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL).
[b]Normal range for hemoglobin: Female 11.2–15.5 and males 12.5–16.2.

TABLE 2 Best hematologic response to therapy by IMWG criteria (n = 28)

Response	n (%)
VGPR or better	26 (93)
sCR	15 (54)
CR	3 (11)
VGPR	8 (29)
PR	2 (7)

Abbreviations: CR, complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

response (Renal PR), if eGFR <15 ml/min/1.73 m^2 prior to treatment improves to 30–59 ml/min/1.73 m^2; minor response (Renal MR), if eGFR <15 ml/min/1.73 m^2 prior to treatment improves to 15–29 ml/min/1.73 m^2 or if eGFR 15–29 ml/min/1.73 m^2 prior to treatment improves to 30–59 ml/min/1.73 m^2; or renal progression, if there is a >25% decrease in eGFR or > 50% increase in 24-hour urine protein (to >1 g/24 h).[26] Amyloid renal response was defined as either reduced proteinuria by ≥50% or a drop in proteinuria to <0.5 g/24 h in those with >0.5 g/24 h at baseline and stable renal function (i.e., ≤ 25% increase in eGFR).[27–29] For patients with eGFR <50 ml/min/1.73 m^2 and proteinuria (>1 g/24 h) as the main presentation of the disease, both sets of criteria defined above were used for response evaluation.

2.4 | Statistical analysis

Categorical patient characteristics were summarized by frequency (percentage) and continuous characteristics were summarized by median and interquartile range (IQR). Time to renal response (TRR, defined as time between start of therapy to time of best response) and renal survival time (RST, defined as time between start of therapy to hemodialysis) were evaluated by the Kaplan–Meier method.

Associations between patient characteristics (including baseline characteristics, treatment characteristics, and HRs) and time-to-event outcomes were assessed by log-rank. The effects of patient and disease characteristics on TRR and RST were estimated by univariate Cox proportional hazard model with $p < .05$ being considered significant. All statistical analyses were performed using R.

3 | RESULTS

3.1 | Patient characteristics

Between January 1999 and January 2016, we identified 54 patients with a diagnosis of MIDD at MSK and NYPH-Cornell, 34 of whom received treatment and met criteria for inclusion in this series. Among these 34 patients, 25 (74%) met criteria for symptomatic multiple myeloma requiring therapy, 3 (9%) met criteria for smoldering multiple myeloma (SMM), and 4 (12%) for monoclonal gammopathy of undetermined significance (MGUS), using IMWG criteria excluding reduced eGFR <40 ml/min or serum creatinine >2 mg/dL as diagnostic criterion.[30] One (3%) patient had chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and 1 (3%) had Waldenstrom macroglobulinemia in addition to MGUS. One (3%) patient had evidence of extrarenal involvement (cardiac and liver) in addition to renal damage, although investigations to uncover extrarenal involvement were not performed systematically in most patients.

Baseline characteristics of the 34 patients at diagnosis are shown in Table 1. Patients had a median age of 49.5 years (IQR, 44–59), 20 (59%) were male, and 23 (68%) had hypertension. Baseline hematologic characteristics included: kappa light chain isotype in 31 (91%) patients; median involved FLC level 129.3 mg/dL (IQR, 31.9–291); median serum free-light-chain ratio (involved/uninvolved) 69.3 (IQR, 14.2–206); M-spike detectable by serum protein electrophoresis (median 0; IQR, 0–0.30) in 11 (32%) patients; median bone marrow

TABLE 3 Best Renal response to therapy

		IMWG Renal response criteria (n = 28)					
		Not Assessable	Renal CR	Renal PR	Renal MR	No Response	Total
Amyloid criteria (n = 28)	Not assessable	0	1	3[a]	3[a]	6[b]	13
	Response	6	2	1	5	0	14
	No response	0	0	0	0	1	1
Total		6	3	4	8	7	28

Abbreviations: CR, complete response; MR, minor response; PR, partial response.
[a]Including 1 patient who came off dialysis.
[b]Including 5 patients who remained on dialysis.

plasmacytosis 20% (IQR, 12.8–30); evidence of myeloma-related lytic bone disease on imaging in 9 (26%) patients; median serum albumin 3.95 g/dL (IQR, 3.5–4.2); median $\beta2$ microglobulin 5.6 mg/L (IQR, 4.5–8.7); and median lactate dehydrogenase 196 U/L (IQR, 168–216). Baseline renal characteristics included: median eGFR by CKD-EPI 23.2 (IQR, 10.9–42.1); median proteinuria 2700 mg/24 h (IQR, 525.2–5840); nephrotic-range proteinuria (≥3 g/24 h) present in 15 (44%) and hematuria in 5 (15%); and dialysis required at presentation prior to initiation of therapy in 7 (21%) patients.

Among the 28 patients whose renal response could be fully assessed before and after treatment, initial renal presentations included: proteinuria >1 g/24 h with preserved eGFR (n = 6, 21%), proteinuria and decreased eGFR (<50 ml/min/1.73 m^2) (n = 9, 32%), and decreased eGFR <50 ml/min/1.73 m^2 without significant proteinuria (>1 g/24 h) (n = 13, 46%). Some patients were on dialysis at initial presentation or shortly after prior to therapy (n = 7, 25%).

3.2 | Treatment characteristics

The first-line therapies used included bortezomib (n = 19; 56%), lenalidomide (n = 7; 21%), cyclophosphamide (n = 9; 26%), dexamethasone alone (n = 5; 15%), and ASCT as part of consolidation therapy (n = 23; 68%) (Table 1). Four patients received solid organ transplantation after their diagnosis with MIDD, including 3 receiving renal allografts and 1 receiving a liver allograft. Two patients required subsequent therapy for recurrent MIDD after organ transplantation but maintained allograft function. Seven patients required hemodialysis at initial diagnosis or shortly after diagnosis but before treatment.

3.3 | Outcome measurements

The median patient follow-up was 110 months. HRs, evaluable in 28 of 34 patients at completion of first-line therapy, were sCR (n = 15, 54%), CR (n = 3, 11%), VGPR (n = 8, 29%), and PR (n = 2, 7%) (Table 2).

Renal responses were evaluable in 28 patients; 22 (79%, including 7 patients on dialysis at diagnosis) had decreased eGFR at baseline and could be assessed by IMWG renal response criteria, while 6 (21%)

had an eGFR >50 ml/min/1.73 m^2 at baseline and could not be assessed using these criteria (Table 3 and Figure S1). Among the 22 patients assessed by IMWG criteria, 15 (68%) had a response, including 3 (14%) Renal CR, 4 (18%) Renal PR, and 8 (36%) Renal MR, while 7 (32%) had no response. Among the 7 patients on dialysis at baseline, 3 remained on dialysis despite treatment, while 4 stopped dialyses after treatment, 2 as a result of the treatment (considered responders by IMWG) and 2 after receiving a transplanted renal allograft (considered non-responders by IMWG).

Among the 28 evaluable patients, 15 (54%) could be assessed using the amyloid criteria since they had significant proteinuria (>1 g/24 h) at baseline, while 13 (46%) could not be assessed using these criteria, including 7 patients on dialysis and 6 without significant proteinuria at baseline (<1 g/24 h) (Table 3 and Figure S1). Among these 15 patients assessed by amyloid criteria, 14 (93%) had a response. Among 9 patients who could be assessed by both criteria, all had concordant results using IMWG or amyloid criteria. A composite response assessment based on both IMWG and amyloid criteria showed that 22 of 28 (79%) assessable patients had a renal response.

3.4 | Dynamics of renal response and survival

With a median follow-up of 110 months, the estimated median overall survival was 136 months (95% CI: 79–NR). Eighteen of 28 patients were alive according to available follow-up at the data cutoff date of May 7, 2021. The median time to best renal response from initiation of treatment was 27 months (95% CI:18–105) (Figure 1A,C), showing that, for some patients, the renal function continues to improve for several years after the start of therapy. When censoring patients who died without requiring dialysis, the median renal survival has not been reached (95%CI: NR–NR) at the end of the study. Two patients who were not on dialysis at the start of treatment progressed to end-stage renal disease (ESRD) and required dialysis during the follow-up period. These patients developing ESRD meet this outcome rather early, although the number of events is small in this cohort (Figure 1B,C).

By univariate analysis baseline beta-2 microglobulin ($\beta2M$) at diagnosis was a factor associated with renal response (p = .04). eGFR at diagnosis was a factor with suggestive evidence (p < .07) with all three quartiles having similar positive effect on renal response
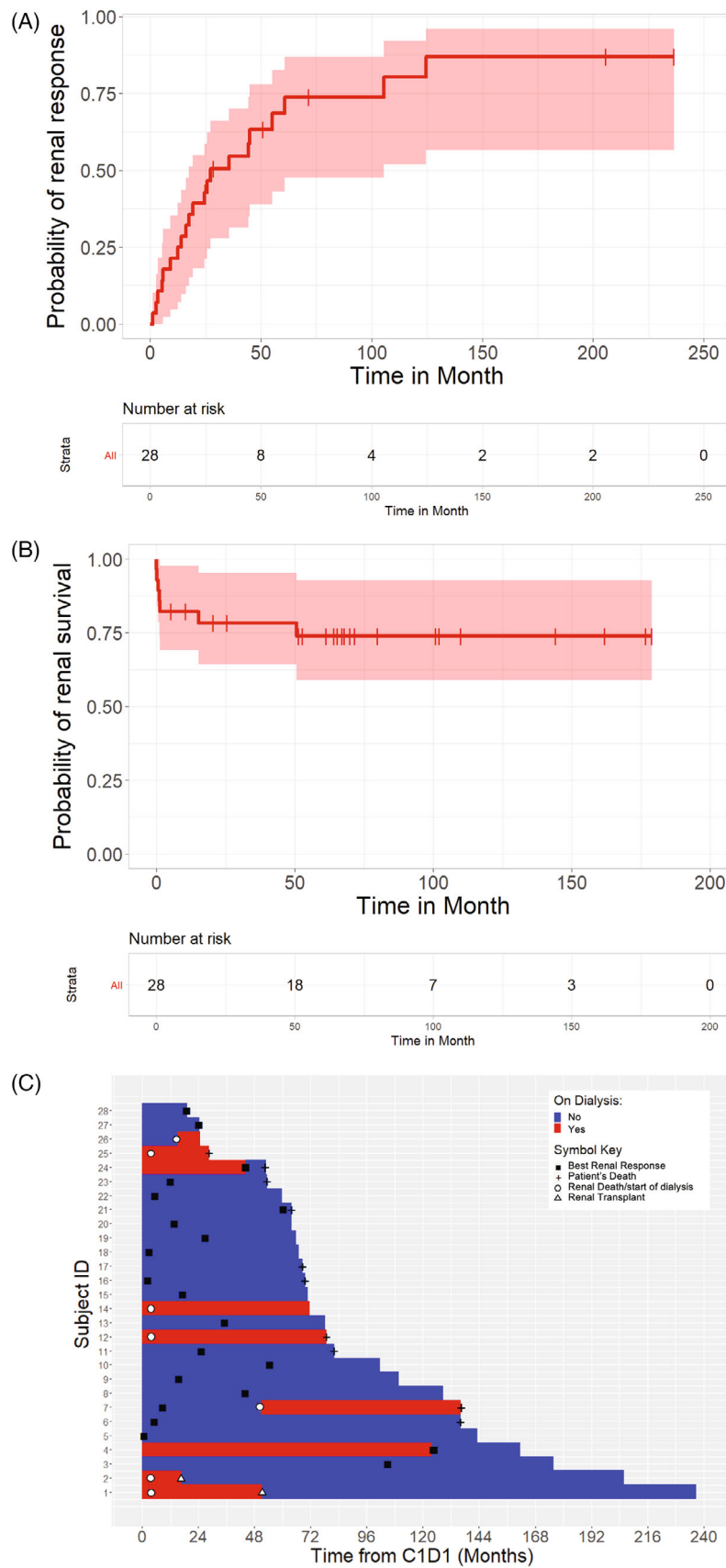
FIGURE 1 Renal response. (A) Time to best response from start of therapy. (B) Duration of response from start of therapy. (C) Swimmer plot illustrating, for each patient, time to best renal response, time to renal death, and time to last assessment or patient's death [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Factors associated with Renal response

Variable	HR	p-value
Age (Quartiles)		.86
45.5–50	0.67 (0.21,2.15)	
50–60.75	0.87 (0.25,3.03)	
>60.75	0.61 (0.16,2.34)	
Gender (M/F)	0.85 (0.35,2.02)	.70
Race (Caucasian/African American)	1 (0.29,3.46)	.99
Hypertension (No/Yes)	1.11 (0.43,2.87)	.83
Involved serum free light chain isotype (K/L)	0.68 (0.15,3.04)	.52
MIDD subtype (HCDD/LCDD/LHCDD)		.33
LCDD	0.38 (0.08,1.73)	
LHCDD	0.91 (0.08,10.25)	
		.75
Involved FLC level (quartiles)	1.13 (0.31,4.09)	
29–105	1.89 (0.53,6.8)	
105–240	1.04 (0.24,4.43)	
>240		
Involved/Uninvolved FLC ratio (quartiles)		.77
12.78–66.66	1.48 (0.42,5.24)	
66.66–203.58	1.86 (0.45,7.66)	
>203.58	1.02 (0.26,4.02)	
		.51
Serum M-protein level (quartiles)	0.49 (0.13,1.82)	
0.05–0.48	1.05 (0.34,3.24)	
>0.48		
Bone marrow plasmacytosis (quartiles)		.36
12.5–20	1.47 (0.54,4.02)	
20–29	1.43 (0.17,12.26)	
>29	0.47 (0.12,1.84)	
Serum albumin level (quartiles)		.42
3.5–3.9	1.29 (0.36,4.65)	
3.9–4.2	1.27 (0.41,3.99)	
>4.2	0.42 (0.1,1.74)	
Beta 2 microglobulin level (quartiles)		**.04**
4.4–5.5	0.74 (0.23,2.43)	
5.5–9.01	0.98 (0.27,3.6)	
>9.01	0.13 (0.03,0.66)	
Estimated GFR at diagnosis (quartiles)		**.07**
10.925–23.2	4.7 (1.15,19.22)	
23.2–42.1	3.13 (0.73,13.41)	
>42.1	4.98 (1.25,19.8)	
Dialysis prior to treatment (Yes/No)	0.06 (0.01,0.47)	**.0004**
24-h urine protein at diagnosis (quartiles)		.49
469.25–2488.95	0.85 (0.24,2.93)	
2488.95–6002.9	1.96 (0.59,6.5)	
>6002.9	1.5 (0.43,5.26)	

Variable	HR	p-value
Hematuria at diagnosis (Yes/No)	1.56 (0.51,4.81)	.43
Bortezomib-based therapy (Yes/No)	1.63 (0.61,4.34)	.32
Lenalidomide-based therapy (Yes/No)	0.9 (0.26,3.14)	.87
ASCT (Yes/No)[a]	0.83 (0.3,2.29)	.72
Hematologic response (CR vs. < CR)[a]	0.62 (0.25,1.54)	.29

Note: Positive HR is associated with increased probability of response. The bold numbers indicate the statistically significant values.

Abbreviations: ASCT, autologous stem cell transplantation; FLC, free light chain; GFR, glomerular filtration rate; HCDD, heavy chain deposition disease; HR, hazard ratio; IQR, interquartile range; K/L, kappa/lambda; LCDD, light chain deposition disease; LHCDD, light and/or heavy chain deposition disease; MIDD; monoclonal immunoglobulin deposition disease; MGUS, monoclonal gammopathy of undetermined significance; MGRS, monoclonal gammopathy of renal significance.

[a]Time-dependent covariate.

compared to the first quartile (eGFR level below 10.92). When combining quartiles two, three, and four into a single category, eGFR was associated with renal response ($p = .02$). Likewise, beta-2 microglobulin and eGFR at diagnosis were factors strongly associated with renal survival ($p = .01$ and $p = .02$, respectively). HR (CR vs. non-CR) was not associated with renal response or survival in this cohort (Table 4).

4 | DISCUSSION

In this retrospective cohort study of patients with MIDD, 33 of 34 (97%) patients had a plasma cell dyscrasia, with 25 (74%) patients meeting the 2014 IMWG criteria for the diagnosis of symptomatic multiple myeloma, 3 (9%) SMM and 4 (12%) MGUS.[30] One patient had a B-cell malignancy associated with an immunoglobulin paraprotein (CLL) and 1 patient had Waldenstrom macroglobulinemia in association with a plasma cell dyscrasia. Note that the high rate of associated multiple myeloma in this series probably reflects the referral bias of a patient population seen in a cancer center. Among the 28 patients whose hematologic data could be fully assessed, we observed a high rate of HR (64% ≥ CR, 93% ≥ VGPR) as the best response to upfront treatment regimens. A high percentage of patients was treated with bortezomib-based regimens and melphalan-based ASCT, consistent with prior reports showing these treatment modalities to be highly effective for the management of patients with MIDD.[9,13–22]

Given that the loss of renal function accounts for the main morbidity for patients with MIDD, we were interested in examining the renal responses to the treatments directed at the underlying neoplasm and analyzing the factors associated with renal response and survival. Despite increasing awareness of the contribution of monoclonal gammopathies to renal injury in patients with MIDD and MGRS in general, post-treatment renal outcomes in patients with MIDD have not been uniformly analyzed in the limited retrospective case series published[5–12] and prospective randomized trials with renal response as the primary objective have not been performed. Furthermore, while assessment of HR is standardized and reported according to the well-established IMWG criteria,[24] there are no standard renal response criteria universally adopted for MGRS, or MIDD specifically.

The standardized amyloid response criteria, predominantly based on proteinuria and widely adopted by consensus and validated in the context of amyloidosis,[27–29] are often used in MGRS, including MIDD, to assess renal response. However, renal dysfunction caused by MIDD is distinct from that caused by amyloid deposition, such that these criteria may have limited applicability. Compared with the amyloidosis population, among patients with MIDD, proteinuria is less common and reduced eGFR is most often the presenting clinical manifestation. Among 28 patients whose renal response was fully assessed, we report only 15 (54%) with significant proteinuria (>1 g/24 h) at baseline; renal response could not be assessed by the amyloid criteria for the other 13 patients, including 7 on dialysis at initial diagnosis. Likewise, IMWG renal response criteria for multiple myeloma,[26] based on assessing the improvement in eGFR, is also not suitable for all patients with MIDD, some of whom present with proteinuria only and a fully preserved eGFR. Indeed, among the 28 patients in this cohort, 22 (79%), including the 7 patients on dialysis at baseline, had a decreased eGFR, while 6 (21%) presented with normal eGFR but significant proteinuria (>1 g/24 h). Nine patients could be assessed by both sets of criteria, and concordant results were observed in all 9.

Overall, we demonstrated that each set of renal response assessment criteria is inadequate in MIDD when considered alone. Hence, we propose combining IMWG and amyloid renal response criteria to account for changes in both proteinuria and eGFR. Using this composite method in our cohort, we observed renal response, following therapy directed at the underlying clonal neoplasm, in a large proportion of patients with renal impairment from MIDD (22 of 28 patients; 79%), including 2 of 7 patients requiring hemodialysis at diagnosis who were able to discontinue dialysis.

Kastritis et al. previously reported the ratio of 24 h proteinuria to eGFR as a sensitive marker of renal risk in patients with amyloidosis. This ratio accounts for changes in both proteinuria and eGFR.[31] In their study, 24-hour proteinuria/eGFR ratio < 30 mg/mL/min/1.73 m^2 was associated with a 2-year progression to dialysis rate of 0% compared to 9% for a ratio of 31 to 99 and 35% for a ratio > 100

($p < .001$). A reduction of this ratio by ≥25% or to <100 (if initially >100) at 3 months was associated with a 2-year progression to dialysis rate of 0% versus 24% for patients not meeting these criteria ($p < .001$). While we were unable to confirm these findings due to our small cohort size, we observed that 2 patients who reached ESRD (not including those requiring hemodialysis upfront) had the highest 24 h proteinuria/eGFR ratio at diagnosis among all 28 patients. This observation should be confirmed and validated in large cohorts. It is worth noting that the 24 h proteinuria/eGFR ratio was used in Kastritis's study as a prognostic factor rather than a tool for measuring renal response.

Interestingly, among the patients with preserved baseline eGFR, who could *only* be assessed by amyloid criteria, all 6 (100%) had a renal response. In contrast, among the 13 patients who could *only* be assessed by IMWG criteria, only 7 (53%) had a renal response. Likewise, among the 15 patients who could be assessed by the amyloid criteria, 14 (93%) had a response while among the 22 patients who could be assessed by IMWG criteria, 15 (68%) had a response. This observation suggests that proteinuria is an early manifestation of the disease likely associated with reversible renal damage.

We also noted that the IMWG renal response criteria may lack granularity for assessing response in patients with mild-to-moderate renal insufficiency (eGFR 30–60 ml/min/1.73m^2). These patients are classified together in these response criteria. For example, a patient whose eGFR improves from 31 to 59 ml/min/1.73m^2 would be considered a non-responder according to the present IMWG criteria. We propose to segregate eGFR levels of 30–45 ml/min/1.73m^2 and 45–60 ml/min/1.73m^2 to enhance the resolution of the IMWG response criteria (Figure S2). In our proposed simplified model, a Renal MR denotes eGFR improvement by one category and a Renal PR by two categories, while a Renal CR denotes full renal recovery (eGFR >60 ml/min/1.73m^2), regardless of the baseline eGFR.

In this series, risk factors associated with renal response and renal survival included baseline eGFR and β2 microglobulin, consistent with previous reports.[9,12] These observations confirm that early diagnosis and treatment are crucial to salvaging renal function and reversing further glomerular filtration damage. The renal survival time curve also confirms prolonged renal survival in most patients, except for those losing renal function early in the course of disease, which may be explained by delayed diagnosis (Figure 1B). HR (CR vs. non-CR or ≥ VGPR vs. < VGPR) was not associated with renal response ($p = .66$) in this cohort, in contrast with most previous reports.[8,9,12] This discrepancy almost certainly results from the small number of patients who achieved <VGPR by hematologic criteria in this series, hindering our ability to detect such an association.

In summary, we observed in this retrospective study a high rate of HR to upfront treatment regimens, which is likely attributable to the wide use of bortezomib-based regimens and ASCT. We also observed a large proportion of patients whose renal impairment from MIDD improved significantly after receiving therapy directed at the underlying clonal neoplasm, with 79% achieving a renal response, including 2 out of 7 patients on hemodialysis at diagnosis discontinuing hemodialysis after treatment. Most importantly, we highlight the disparity in the assessment of renal response encountered in the literature and show that IMWG and amyloid renal response criteria are both essential to adequately assess the renal response in MIDD. We, thus, emphasize the need to develop consensus renal response criteria for this disease, and our study informs the development of such criteria. Given the scarcity of outcome data in MIDD, especially in the era of novel anti-myeloma therapy, prospective studies using uniform renal response criteria are needed to optimize the management of these patients.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

Hani Hassoun received consultancy fees and honoraria from Novartis; received research funding from Celgene and Takeda Pharmaceuticals; and served on the advisory committee for Takeda Pharmaceuticals. *Heather J. Landau* served on the advisory committee for Takeda Pharmaceuticals, Celgene, Janssen Pharmaceuticals, Sanofi, and Caelum Biosciences; received honorarium from Sanofi; and received research funding from Takeda Pharmaceuticals. *Neha Korde* received research funding from Amgen and Jansen Pharmaceuticals; and consulting fees from Clinical Care Options, Physician Education Resources, and Cancer Network. *Sham Mailankody* received funding from Allogene Therapeutics, Takeda Oncology, Juno Therapeutics, Bristol Myers Squibb, Janssen Oncology, and Fate Therapeutics; has served on an advisory panel for Legend Biotech, Evicore, Janssen Oncology, BioAscend; and has received honoraria from Plexus Communication, OncLive, and Physician Education Resource. *David J. Chung* has received research funding from Genetech. *Malin Hultcrantz* has received research funding from GSK, Amgen, Daiichi Sankyo, consulting fees from Curio

DATA AVAILABILITY STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.