Assessment of Renal Outcome Following Therapy in Monoclonal Immunoglobulin Deposition Disease (MIDD): A Retrospective Study Highlighting the Need for Consensus Criteria

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Introduction

- Randall-type Monoclonal immunoglobulin Deposition Disease (MIDD) is a rare condition in which organ dysfunction arises from monoclonal heavy and/or light chains deposition along basement membranes, and predominantly affects the kidneys. MIDD is among the most common subtypes of monoclonal gammopathies of renal significance (MGRS) and is associated with plasma cell and lymphoid neoplasms.
- Hematologic responses are characterized according to IMWG International Myeloma Working Group (IMWG) consensus criteria.
- Although two renal response systems exist for plasma cell disorders, the IMWG and Amyloidosis Criteria, which each evaluate improvements in glomerular filtration rate and proteinuria, respectively, **there are no consensus response criteria for evaluating organ responses to treatment for MIDD**.

Objectives

- To examine treatment outcomes in MIDD using modern plasma-cell directed therapy and evaluate hematologic and renal response to therapy according to existing response criteria.
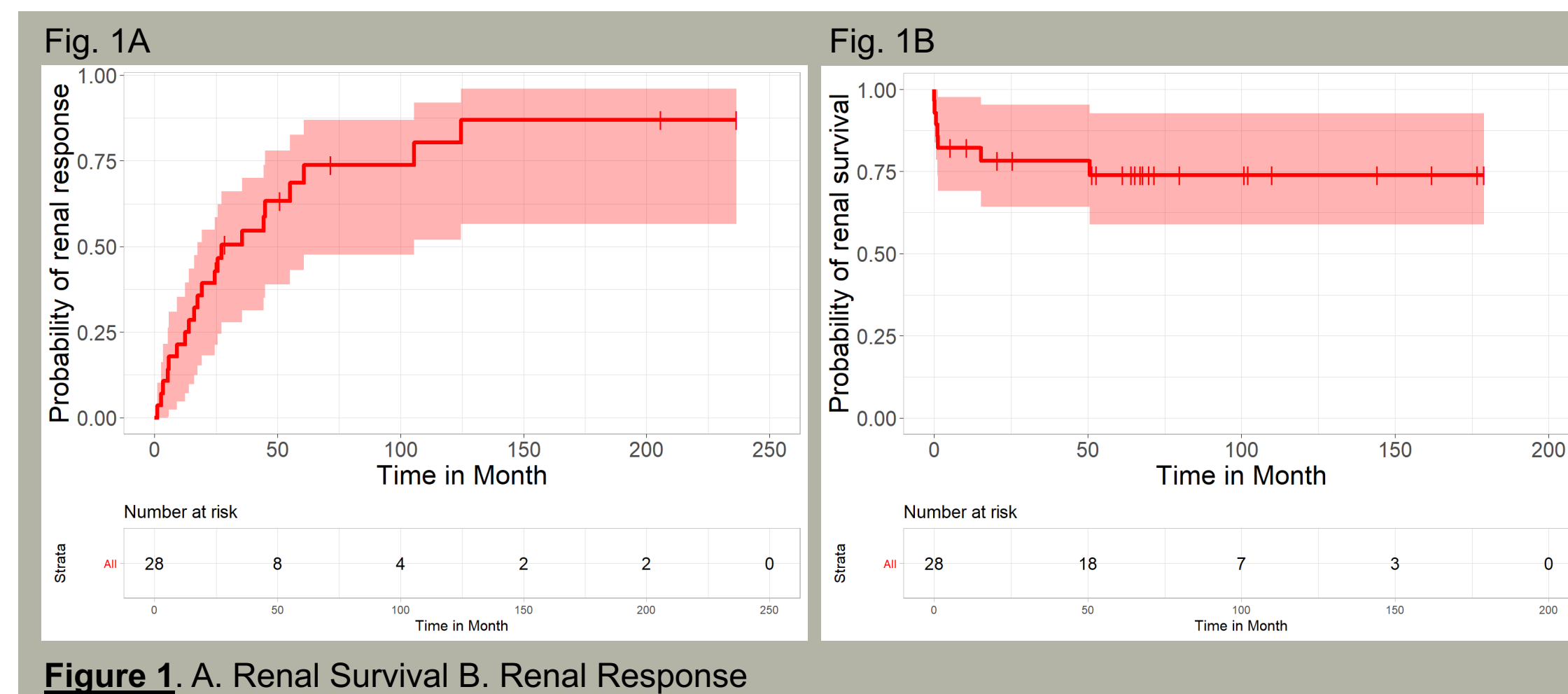
Methods

- Retrospective cohort study, including patients with biopsy-proven MIDD who received treatment at Memorial Sloan Kettering Cancer Center or New York Presbyterian Hospital/Weill Cornell Medical Center
- Collected demographic, clinical, and treatment history, laboratory results including hematologic parameters, renal function (estimated glomerular filtration rate by CKD-EPI), and proteinuria evaluation, overall survival, renal survival (time to onset of renal replacement therapy).
- Renal Response (RR) criteria used were the IMWG RR criteria based on eGFR for pts with decreased eGFR <50mL/min/1.73 m² with or without significant proteinuria (>1 g/24 h) or amyloid response criteria for pts with significant proteinuria with or without preserved eGFR, at presentation. Patients achieving response by one or more criteria were deemed to have a RR.
- Categorical pts characteristics were summarized by frequency (%) and continuous characteristics by median and interquartile range. Time to best RR (time from start of Rx to best response) and renal survival (time from start of Rx to hemodialysis) were evaluated by Kaplan-Meier method. Associations between pts characteristics and time to response outcome were assessed by log-rank. The effects of baseline characteristics on RR were estimated by univariate Cox proportional hazard model.

Results

Table 1

Age (median, IQR)	49.5 (44–59)
Sex, n (%)	
Male	20 (59)
Female	14 (41)
Race, n (%)	
White	28 (82)
African American	6 (18)
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)
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	28 (82)
MGUS	4 (12)
Chronic lymphocytic leukemia	1 (3)
Waldenstrom macroglobulinemia + plasma cell dyscrasia	1 (3)
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)
24-hr 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)

Table 2: Hematologic Response per IMWG MM Uniform Response Criteria

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

VGPR, Very Good Partial Response; sCR, stringent Complete Response; PR, Partial Response

Figure 1. A. Renal Survival B. Renal Response

	IMWG Renal Response Criteria	**Amyloidosis Response Criteria**
CR$_{Renal}$	GFR ≥ 60 ml/min/1.73 m²	**Renal Response =** >50% decrease (at least 0.5 g day⁻¹) of 24-hr urine protein (urine protein must be >0.5 g day⁻¹ pretreatment) without worsening of creatinine and creatinine clearance by 25% over baseline.
PR$_{Renal}$	GFR from <15 mL/min/1.73 m² at baseline increases to 30–59 mL/min/1.73 m², or	
MR$_{Renal}$	GFR increase: 1) either from <15 mL/min/1.73 m² at baseline to 15–29 mL/min/1.73 m² OR 2) from 15–29 mL/min/1.73 m² at baseline to 30–59 mL/min/1.73 m².	
Renal Progression	> 25% decrease in eGFR or > 50% increase in 24-hour urine protein (to >1 g/24 h).	

Table 3: Comparison of Responses by IMWG vs. Amyloid Criteria

		IMWG Renal Response Criteria (n=28)					**Total**
		Not Assessable	CR	PR	MR	No Response	
Amyloid Criteria (n=28)	Not Assessable	0	1	3*	3*	6**	13
	Response	6	2	1	5	0	14
	No Response	0	0	0	0	1	1
Total		6	3	4	8	7	28

Patients Assessable by Amyloid criteria: 6, 9, 13 Patients Assessable by IMWG criteria
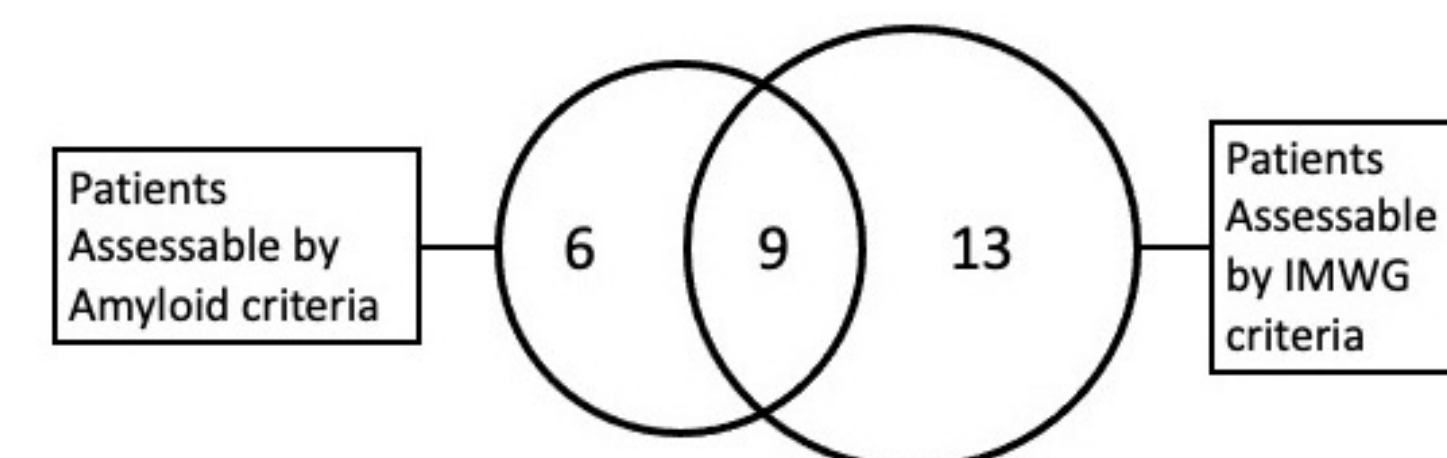
Results (continued)

- With most pts treated with bortezomib and autologous stem cell transplantation (ASCT), 26 of 28 (94%) achieved ≥ VGPR

- We demonstrate that both IMWG (based on eGFR) and amyloid (based on proteinuria) criteria are needed to capture RR: Among 28 pts whose RR could be assessed, initial renal presentations included proteinuria with preserved eGFR (n=6, 21%), proteinuria and decreased eGFR (n=9, 32%), and decreased eGFR without proteinuria (n=13, 46%).

- Using both criteria, which were concordant in pts with both decreased eGFR and proteinuria, 22 of 28 pts (79%) had a RR, including 2 of 7 discontinuing dialysis. All 6 pts (100%) with isolated proteinuria and 7 of 13 (54%) with isolated decreased eGFR achieved RR, suggesting that isolated proteinuria may be an early and reversible manifestation of MIDD.

- Baseline eGFR was predictive of RR (p<0.02 by quartile), while hematologic response (CR vs. non-CR) was not, probably due to high hematologic response rates, hindering the ability to detect such association.

- With a median-follow up of 110 months (95% CI: 71-NR), the median overall survival was 136 months (95% CI: 79–NR) and median RS had not been reached.

Conclusions

- We have used a systematic approach to assess RR in MIDD, a field that remains mired in uncertainty in the literature.
- We show that IMWG and amyloid response criteria are both essential to adequately assess the RR in MIDD. We also show that the RR rate is high and durable in this disease with bortezomib-based treatment and ASCT.
- This study will help inform the development of consensus renal response criteria that are needed in MIDD.

References

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