

***Profile of Light Chain Amyloidosis in Waldenström's Macroglobulinemia***

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***Understanding Amyloidogenesis in Sub-types of Light Chain Amyloidosis***

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## IgM Amyloidosis

- Waldenström's Macroglobulinemia (WM) and other IgM gammopathies can be associated with local or systemic amyloidosis (AL)
- Unclear if this is a biologic distinct entity or more similar to WM or AL
- Prevalence is ~ 5-7% of AL patients (Ig M) and ~3% of WM patients

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## Current Literature

- IgM amyloidosis associated with lower cardiac involvement vs. non-IgM amyloidosis.
- More lung, soft tissue and nerve involvement.
- Unique prognostic factors: Liver and nerve involvement

Gertz et al. *J Clin Oncol* 11(5): 914-920.  
Wechalekar et al. *Blood* 112(10): 4009-4016.  
Milani et al. *Best Pract Res Clin Haematol* 29(2): 241-248.  
Palladini et al. *Clin Lymphoma Myeloma* 9(1): 80-83.  
Sachchithanatham, S. et al. *J Clin Oncol* 34(17): 2037-2045.

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## Our Data

- Patients with systemic AL amyloidosis diagnosed between 2006-15
- Patients with active myeloma (lytic lesions) excluded
- IgM amyloidosis: 6.6% (74/1127)

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### Baseline Characteristics IgM amyloidosis

Characteristic	IgM (N=74) (Median, IQR)	Non-IgM (N=1053) (Median, IQR)	P-value
Age Diagnosis (Years)	68	64	<b>0.0004</b>
Males (%)	76	65	0.05
iLC- Lambda	64	76	<b>0.03</b>
BM plasma cells (%)	10	10	0.1
serum M-protein, g/dL	1 (0.6-1.5)	0 (0-0.6)	<b>&lt;0.001</b>
dFLC, mg/dL	12.5	22.7	<b>0.0002</b>
eGFR (calculated - MDRD)	69	62	0.3
24 hour urine protein, mg	675	1135	0.6
Troponin-T	0.01	0.03	0.07
NTProBNP	1575.5	3535	<b>0.005</b>
Mayo 2012 stage (%)	36/21/21/21	22/22/25/30	0.07
Mayo 2004 Stage (%)	32/35/33	19/37/44	<b>0.05</b>
T(11;14)	9/27 (33%)	309/629 (49%)	0.1
Trisomy/tetrasomy	2/24 (8%)	151/631 (24%)	0.08

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### Organ Involvement

Characteristic	IgM (N=74) %	Non-IgM (N=1053) %	P-value
<b>Cardiac</b>	<b>61</b>	<b>75</b>	<b>0.008</b>
Renal	54	59	0.4
Renal Stage 1/2/3	57/25/17	52/38/10	<b>0.04</b>
Liver	10	17	0.09
Gastrointestinal	19	24	0.3
Autonomic NS	12	12	0.9
<b>Multi-organ involvement</b>	<b>44</b>	<b>60</b>	<b>0.007</b>

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## Response to Therapy

Characteristic	IgM (N=49)	Non-IgM (N=843)	P-value
Transplant based Rx	14/49 (29)	268/843 (32)	0.6
<b>HEME RESPONSE (dFLC)</b>			
Overall response ( $\geq$ PR)	<b>19/30 (63)</b>	<b>454/561 (81)</b>	<b>0.02</b>
Overall VGPR	14/30 (47)	324/561 (58)	0.2
VGPR at 6 months	10/39 (26)	270/660 (41)	<b>0.06</b>
VGPR at 12 months	11/34 (32)	268/633 (42)	0.3
<b>ORGAN RESPONSE</b>			
Cardiac response 6 months	0/21 (0)	78/425 (18)	<b>0.03</b>
Cardiac response 12 months	2/21 (19)	100/431 (23)	0.2
Renal response 6 months	4/19 (21)	134/383 (35)	0.3
Renal response 12 months	4/17 (24)	166/388 (43)	0.1
Liver response 6 months	0/5 (0)	16/105 (15)	-
Liver response 12 months	0/5 (0)	24/103 (23)	-

Response rates at landmark time-points are intent to treat;  
Overall response rates do not include patients who died before assessment in denominator

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## Cox Proportional Hazards Model

	Univariate (all)	Univariate (IgM pts)	MV Model 1	MV Model 2	MV Model 3
IgM vs. non-IgM	-	-	<b>1.8 (1.2-2.6), p=0.008</b>	<b>1.9 (1.2-2.8), p=0.005</b>	<b>1.8 (1.2-2.6), p=0.007</b>
Mayo Stage (1/2/3/4)	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Transplant	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
eGFR	P<0.001	P=0.0005	p=0.99	-	-
24 hour urine protein	P<0.001	P=0.2	P=0.95	-	-
BM plasma cells > 10%	P=0.0002	P=0.04		p=0.8	
Liver involvement	p<0.001	P=0.003			
Kidney involvement	p<0.001	P=0.3			
Serum M protein $\geq$ 1	-	0.1			

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### Cox Proportional Hazards Model: IgM Amyloidosis only

	Hazard Ratio; p value
Liver involvement	<b>5.9 (1.7-17.7) P=0.002</b>
Mayo Stage (1/2/3/4)	P=0.004
Transplant	P=0.02

- Another model: Liver involvement remained significant in IgM amyloidosis, even after accounting for renal and cardiac involvement.

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## Conclusions

- Patients with IgM amyloidosis have less cardiac and multi-organ involvement
- Trend towards lower rates of hematologic response
- Trend towards lower rate of organ response
- IgM amyloidosis is an independent risk factor for OS after adjusting for treatment and Mayo Stage
- Liver involvement is a unique prognostic factor, consistent with recent European data

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