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Prognostication in IgM and LPL associated systemic AL amyloidosis

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Introduction:

IgM-associated systemic light-chain amyloidosis (IgM-AL) is a distinct clinical entity, accounting for up to 7% of systemic AL. Despite the expansion of novel therapies, deep clonal responses are rare. We previously reported small series using bendamustine-rituximab (BR) in IgM-AL but the largest series evaluating predictors of overall survival (OS) was in an era prior to widespread use of BR. We reviewed outcomes in IgM-AL in the modern treatment era.

Methods:

Patients enrolled in a prospective observational study at the United Kingdom National Amyloidosis Centre from 2012–2024 treated for systemic AL were reviewed. Patients with a serum IgM-AL or lymphoplasmacytic lymphoma (LPL) in the bone marrow were included. Ethical approval was obtained (REC: 09/H0715/58).

Results:

Two-hundred-and-twenty-one patients (129 male, 92 female) were included. Baseline characteristics are shown in Table 1. Median age at presentation was 70 years (range 37-89), with 97% White and 1% each Asian, Black, Other/mixed. A median of two organs (range 1-4) were involved: 95 (44%) had cardiac, 141 (66%) renal, 38 (18%) soft tissue and 28 (13%) each liver and peripheral nerve involvement. Sixty-seven percent had lambda AL-type and a median difference in involved and uninvolved free light chain (dFLC) 106mg/L (range 0-5718), monoclonal protein (M-protein) 9g/L (range 0-54) and bone marrow LPL infiltrate 10% (range 0-95).

A median of 1 (range 0-4) line of therapy was delivered after the diagnosis of AL was made. Patients were treated with the following first-line therapies for AL: BR in 97 (44%); bortezomib-cyclophosphamide-dexamethasone $\pm$ rituximab (VCD$\pm$R) in 77 (35%); dexamethasone-

rituximab-cyclophosphamide in 19 (9%), RCHOP-like in 8 (4%), daratumumab-VCD in 4 (2%), zanubrutinib in 2 (1%) and others (14; 6%). None had an autologous stem cell transplant upfront.

Patients were classified by Mayo stages I, II, IIIa and IIIb in 34 (19%), 79 (39%), 57 (28%) and 35 (17%), respectively. At a median follow-up of 46 months (95% CI 35-52), median OS was 58 months (95% CI 32-78) (Figure 1). The estimated one, three and five-year OS was 71% (95% CI 65-77), 56% (95% CI 49-63) and 49% (95% CI 41-57). The median OS by was 72 months (95% CI 27-NR) and 42 months (95% CI 25-71) for BR and VCD±R.

Factors predicting OS in a multivariable model included: age, per year (HR 1.05 [95% CI 1.02-1.08], p=0.001), NT-proBNP, per 1000ng/L (HR 1.05 [95% CI 1.02-1.08], p=0.001), troponin, per 10ng/L (HR 1.04 [95% CI 1.02-1.08], p=0.05), M-protein, per g/L (HR 1.02 [95% CI 1.00-1.05], p=0.04), cardiac involvement (HR 2.44 [95% CI 1.50-3.96], p<0.001), renal involvement (HR 1.65 [95% CI 1.02-2.54], p=0.04) and peripheral nerve involvement (HR 1.98 [95% CI 1.05-3.76], p=0.04). dFLC (p=0.10), free-light chain isotype (κ vs λ, p=0.14) and soft tissue involvement (p=0.26) were not independently prognostic.

Conclusion:

In the modern treatment era, the survival for IgM-AL appears to have improved (58 v 42 months in our previous report n=250) and longer for BR v VCD±R. Survival is still dependant on cardiac involvement and intact IgM M-protein remain independent predictors whilst dFLC is not independently prognostic.

Table 1. Baseline characteristics

Characteristic	n=221
Age, years (range)	70 (37-89)
>65 years	163 (74)
Gender (n, %)	
Male	129 (58)
Female	92 (42)
Ethnicity (n=172)	
White	166 (97)
Black	2 (1)
Asian	2 (1)
Other/Mixed	2 (1)
AL isotype (n, %)	
Lambda	149 (67)
Kappa	72 (33)
dFLC, mg/L (range)	106 (0-5718)
M-protein, g/L (n=214)	9 (0-54)
Bone marrow infiltrate, % (n=79)	10 (0-95)
Involved organs (n=214, %)	
Median (range)	2 (1-4)
Heart	95 (44)
Kidney	141 (66)
Liver	28 (13)
Peripheral nervous system	27 (13)
Soft tissue	38 (18)
Mayo stage (European modification, n=205)	
Stage I	34 (17)
Stage II	79 (39)
Stage IIIa	57 (28)
Stage IIIb	35 (17)
Haemoglobin, g/L (n=210)	121 (63-180)
Creatinine, µmmol/L	93 (34-742)
Estimated GFR ≤20ml/min (n=210)	11 (5)
24 hour urine protein, g (n=158)	2.3 (0-34.6)
Albumin, g/L	33 (14-49)
NT-proBNP, ng/L	1085 (25-70000)
High sensitivity troponin T, ng/L	38 (0-308)
LV septal thickness, mm	12 (8-22)
LVEF, %	60 (32-85)
GLS, % (n=134)	-16.7 (-27.8 - -5.4)
Body mass index, kg/m^2	25 (16-48)
Systolic postural drop ≥20mmHg (n=206)	43 (21)

dFLC, difference in involved and uninvolved free light chain; GLS, global longitudinal strain

Figure 2. Overall survival for patients with IgM-AL and LPL