Rapid hematologic responses improve outcomes in patients with very advanced (stage IIIb) cardiac immunoglobulin light chain amyloidosis

Systemic AL amyloidosis (AL) is caused by deposition of misfolded immunoglobulin light chains, leading to potentially catastrophic visceral dysfunction.[1] Outcomes are heterogeneous, but cardiac involvement is a key survival predictor. Cardiac troponin-T and N-terminal pro-brain natriuretic peptide (NT-proBNP) are sensitive, specific markers of myocyte damage and critically determine prognosis in AL. They form the basis of the widely used Mayo Clinic 2004 cardiac AL staging system.[2]

The initial Mayo study reported that the median overall survival in stage I (NT-proBNP <332 ng/L and troponin-T <0.035 μg/L), stage II (NT-proBNP >332 ng/L or troponin-T >0.035 μg/L) and stage III (NT-proBNP >332 ng/L and troponin-T >0.035 μg/L) AL was 26.4, 10.5 and 3.5 months, respectively.[2] This staging system has been refined, incorporating the difference in involved and uninvolved serum free light chains (dFLC).[3] A European collaboration reported a median overall survival of 7.1 months in stage III and defined an ultra-high risk subgroup with stage IIIb involvement (NT-proBNP >8500 ng/L and troponin-T >0.035 μg/L), associated with the poorest survival (4 months).[4] The initial Mayo study was a retrospective analysis of 242 patients with newly diagnosed AL between 1979-2000; the European study captured patients from 2004-2013. The modest improvement in outcomes in the latter study may be due to the availability of novel agents, disease awareness and improved supportive care. There is a paucity of outcome data in the ultra-high risk stage IIIb subgroup - such patients are generally excluded from clinical trials. We report here the outcomes of 179 patients with stage IIIb cardiac AL, showing that treatment responses can affect survival even in this poor-risk cohort.

All patients from ALchemy (a prospective observational study of all newly diagnosed AL patients at the UK National Amyloidosis Centre) with Mayo stage IIIb cardiac AL (troponin-T >0.035 μg/L and NT-proBNP >8500 ng/L) from 2009-2015 were included. Patients were treated according to nationally agreed protocols in the UK-BSCH guidelines[5] (current protocols available at http://www.ucl.ac.uk/amyloidosis/nac/chemotherapy_protocols). Organ involvement and hematologic and amyloidotic organ responses were assessed according to amyloidosis consensus criteria.[6] Primary outcome measures were overall survival and the impact of hematologic response on survival.

Table 1 shows the baseline characteristics of the 179 patients included in the study. Their median age was 66.3 years (range, 41.4-89.4 years). Forty-four percent had New York Heart Association class 3-4 symptoms and 18% had an Eastern Cooperative Oncology Group score ≥3. The median NT-proBNP was 14762 ng/L (range, 8500-147940 ng/L). The median left ventricular wall thickness was 15 mm (range, 10-21 mm) and median left ventricular ejection fraction (LVEF) was 49% (23-75%). One hundred and thirty-two (73%) had renal involvement and 29 (16%) had liver involvement. Thirty (17%) patients died prior to treatment. These patients were very unwell and opted for supportive care only. First-line treatment included: cyclophosphamide, thalidomide and dexamethasone (CTD) in 27%; cyclophosphamide, bortezomib and dexamethasone (CyBorD) in 39%; bortezomib and dexamethasone in 7%; melphalan and dexamethasone in 2%; lenalidomide and dexamethasone in 1%; and other treatment in 7%.

In the intention-to-treat analysis (including all patients) of hematologic responses at 6 months, 35 patients (20%) had a complete response (CR), 25 (14%) had a very good partial response (VGPR), 32 (18%) had a partial response (PR) and 87 (48%) did not have a response (including those who died prior to/after treatment initiation). Thirty-seven patients (21%) achieved a CR/VGPR by day 30. On an intention-to-treat basis, the median overall survival was 6 months (Figure 1A). Patients in a CR/VGPR by day 30 of treatment had a median overall survival of 26 months, compared to 5 months in those who did not have a CR/VGPR (Figure 1C). The median overall survival in patients with overall CR/VGPR, PR and non-response at 6 months was 38 months, 7 months and 2.6 months respectively (log rank $P<0.0001$) (Figure 1B). A landmark analysis showed that of 76 patients still alive at 6 months who had achieved a CR, VGPR, PR and non-response at 1 month (after 1 cycle of chemotherapy), the proportion alive at 12 months was 86%, 74%, 74% and 33%, respectively. Table 2 shows hematologic responses by treatment. Of patients treated with CTD or CyBorD, 14% and 36% achieved a CR/VGPR at 1 month ($P<0.01$), respectively. The proportion of patients treated with CTD or CyBorD that achieved a CR/VGPR at 6 months was 33% and 52% ($P=0.04$), respectively. There was a suggestion of better overall survival with CyBorD than with CTD but the difference was not statistically significant (possibly due to the small numbers of patients and proportion of CTD patients also achieving a VGPR/better within one cycle) (Figure 1D).

Univariate and receiver operating characteristic curve analysis revealed that LVEF <55%, dFLC >400 mg/L and systolic blood pressure <110 mmHg were predictors of poor survival. The median overall survival for patients with values above/below the threshold was: dFLC < *versus* > 400 mg/L – 7 months versus 3 months; LVEF > *versus* < 55% - 10 months *versus* 5 months; systolic blood pressure > *versus* < 110 mmHg – 10 months *versus* 5 months. In a multivariate model, not achieving a CR/VGPR at 6 months [hazard ratio (HR) 5.3, $P<0.001$; 95% confidence interval (CI): 3.8-8.2], LVEF <55% (HR 1.5, $P=0.044$; 95% CI: 1.05-2.1), dFLC >400 mg/L (HR 1.3, $P=0.076$; 95% CI: 0.9-1.8) and systolic blood pressure <110 mmHg (HR 1.55, $P=0.023$; 95% CI: 1.05-2.1) were independent predictors of mortality.

This study, focusing exclusively on stage IIIb AL, highlights the complex heterogeneity of this disease. There is likely referral bias in the cohort: very unwell patients may be unable to travel to our center. That withstanding, the median overall survival is 6 months, which is slightly better than the survival previously described in patients with advanced cardiac involvement. Stage IIIb AL presents a challenging dichotomy. Half of the patients lived long enough to complete treatment and be assessed for response. Strikingly, those achieving a response by Day 30 or overall CR/VGPR at 6 months had markedly better survival than ever reported in such a cohort of patients. However, the other half of patients died, unable to benefit from treatment - perhaps their disease was too advanced to enable hematologic response to improve survival. The European collaboration identified stage IIIb patients as constituting a separate cohort[4] but patients are heterogeneous. Hypotension, poor systolic function and high level of light chains at presentation (previously reported as poor prognostic factors in AL) were further determinants of survival. The European study reported lower hematologic response rates (32% achieved ≥PR in the intention-to-treat analysis),[4] probably because it included patients from 2002-2010 with a smaller proportion treated with novel agent-based combination therapy compared to the current cohort (7% *versus* 48% treated with a bortezomib-based regime, respective-

ly). Hematologic responses to CyBorD in this cohort are similar to those in a previous multicenter study of stage III patients treated with CyBorD.[7]

These data generate important hypotheses requiring study in prospective trials. The encouraging survival of patients who respond to therapy should engender confidence in designing trials for this cohort of patients, thus far excluded from all prospective AL trials.[6,8] The marked improvement in outcomes for early responders suggests that perhaps in some patients, light chain toxicity is a critical factor that is potentially reversible with chemotherapy-induced hematologic response. Others may have a combination of light chain toxicity and true amyloid deposition that may not be rapidly amenable to chemotherapy to the

Table 1. Baseline characteristics.

n=179 General	Median (range)	Frequency (%)
Median age (range), years	66.3 (41.4 –89.4)	
Male		102 (57%)
Female		77 (43%)
ECOG performance status		
0		0
1		29 (16%)
2		118 (66%)
3		32 (18%)
4		0
Median 6-minute walk test (n=68, metres)	184 (46-651)	
Involved light chain type		
Kappa		38 (21%)
Lambda		141 (79%)
Median dFLC (mg/L)	396 (0.7 - 12788)	
dFLC >400 mg/L		87 (49%)
Median serum monoclonal paraprotein (g/L)	5 (0 – 54)	
Serum paraprotein > 5 g/L		60 (34%)
Organ involvement		
Cardiac involvement		179 (100%)
Renal involvement		132 (73%)
Liver involvement		29 (16%)
Peripheral nerve involvement		12 (7%)
Autonomic involvement		15 (8%)
Soft tissue involvement		31 (17%)
Gastrointestinal tract involvement		10 (6%)
Median serum creatinine (μmol/L)	126 (49-684)	
Median 24 hour urinary protein (g/24 hours)	1.96 (0.1 - 56.8)	
Median serum albumin (g/L)	35 (14-49)	
Median bilirubin (μmol/L)	10 (2-70)	
Median ALP (ULN 129 units/L)	104 (35-1602)	
Cardiac parameters		
New York Heart Association class		
1-2		87 (49%)
3-4		67 (38%)
Not recorded		25 (13%)
Median systolic BP (mmHg)	107 (79-171)	
Systolic BP ≤110 mm Hg		97 (54%)
Median NT-proBNP (ng/L)	14762 (8500-147940)	
NT-proBNP > 8500 ng/L		179 (100%)
Median cardiac troponin T (ng/L)	156 (39 – 874)	
Median left ventricular ejection fraction (%)	49 (23-75)	
Median left ventricular wall thickness (mm)	15 (10-21)	
Left ventricular ejection fraction <55%		128 (72%)

EcCOG: Eastern Cooperative Oncology Group; dFLC: difference in involved and uninvolved free light chains; ALP: alkaline phosphatase; ULN: upper limit of normal; BP: blood pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide.

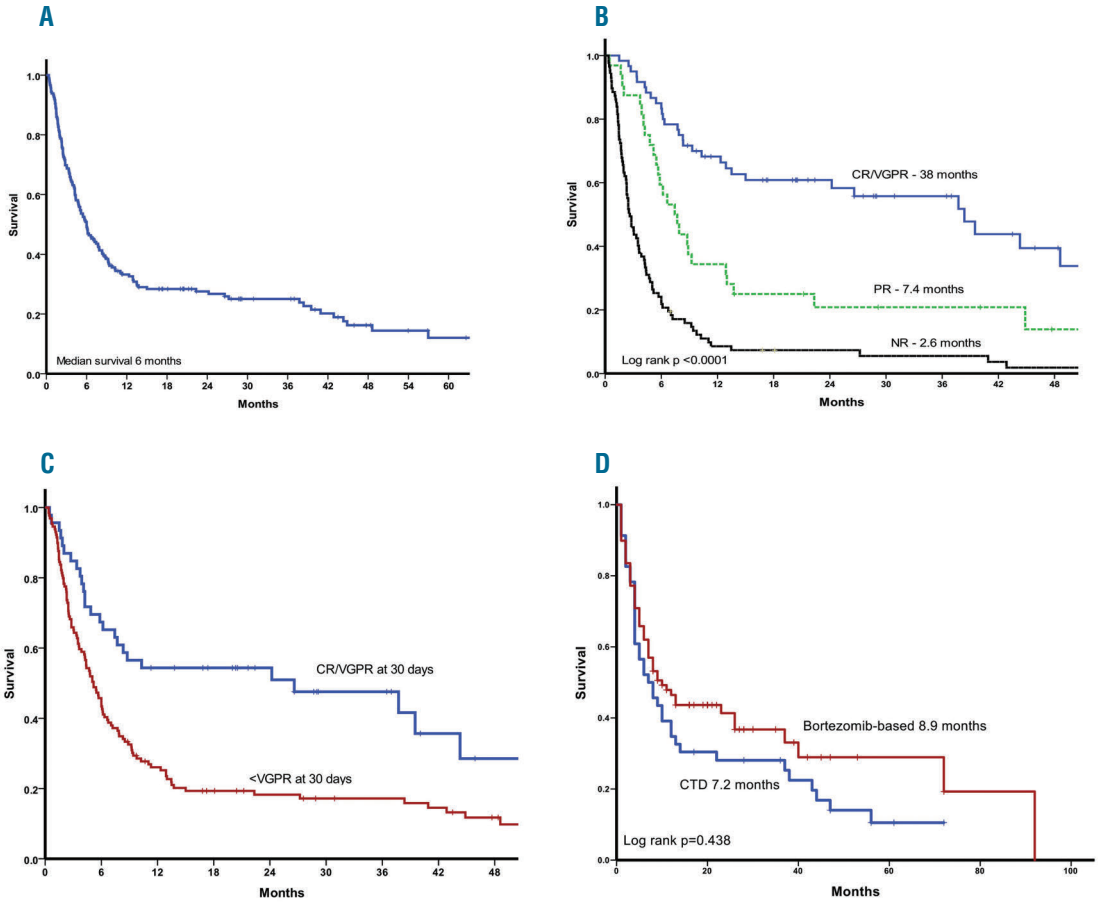

Figure 1. Overall survival of the entire cohort of stage IIIb AL patients, by hematologic response and by treatment. (A) The median overall survival in this group of 179 patients with stage IIIb cardiac immunoglobulin light chain amyloidosis was 6 months. Patients who opted for palliative care and were not treated with chemotherapy (17% of the cohort) are included in this analysis. (B) Median overall survival in those patients who achieved a complete response (CR)/very good partial response (VGPR) or partial response (PR) or did not have a response (NR - including patients who died with or without treatment) was 38 months, 7.4 months and 2.6 months, respectively (log rank *P*<0.0001). (C) Median overall survival in those patients who had a CR/VGPR at day 30 was 26 months, compared to 5 months in patients who achieved less than a VGPR. (D) There was no significant difference in median overall survival between patients treated with bortezomib-based regimes or CTD.

Table 2. Hematologic responses by treatment.

		Hematologic response at 30 days (ITT)					Hematologic response at 6 months (ITT)				
	n	CR	VGPR	PR	Non-response, including deaths	Deaths	CR	VGPR	PR	Non-response, including deaths	Deaths
CTD	48	4 (8%)	3 (6%)	21 (44%)	12 (25%)	6 (13%)	11 (23%)	5 (10%)	13 (27%)	19 (40%)	18 (38%)
CyBorD	70	12 (17%)	13 (19%)	23 (33%)	15 (21%)	9 (13%)	20 (29%)	16 (23%)	12 (17%)	22 (31%)	20 (29%)
Bortezomib, dexamethasone	13	1 (8%)	1 (8%)	5 (38%)	5 (38%)	4 (31%)	3 (23%)	2 (15%)	3 (23%)	5 (39%)	4 (31%)
Melphalan, dexamethasone	4	1 (25%)	0	0	2 (50%)	0	1 (25%)	1 (25%)	1 (25%)	1 (25%)	1 (25%)
Lenalidomide, dexamethasone	3	0	2 (67%)	0	1 (33%)	0	0	1 (33%)	0	2 (67%)	2 (67%)
Other	11	0	0	3 (27%)	8 (73%)	3 (27%)	0	0	3 (27%)	8 (73%)	7 (64%)

CTD: cyclophosphamide, thalidomide and dexamethasone; CyBorD: cyclophosphamide, bortezomib and dexamethasone; ITT: intention-to-treat; CR: complete response; VGPR: very good partial response; PR: partial response.

same extent. Specialist cardiac magnetic resonance imaging with T2 sequences showing edema may help delineate these findings and is part of an ongoing study at our center.

Although rapid hematologic response in 1 month improves survival, the challenge is to guide these fragile patients through chemotherapy, during which toxicity has a high chance of leading to cardiac mortality. Patients not achieving a reduction in dFLC by the end of cycle 1 require review of their chemotherapy regime, with addition of other agents if feasible. In both intention-to-treat and landmark analyses, we found that early response appears to translate into a survival benefit at 12 months. However, hematologic response does not immediately affect amyloidotic visceral dysfunction: patients can succumb to effects of end-organ damage despite excellent hematologic responses. This may partly explain the lack of difference in outcomes with CyBorD or CTD, despite better hematologic responses in the CyBorD group. The small numbers limit utility of subset analysis but larger studies across international centers are planned to validate these results. Given the better early responses, bortezomib-based regimes would still be recommended first-line for these patients.

Treatment regimens offering rapid hematologic responses with minimal toxicity are the holy grail of this disease. Use of genetic markers to identify markers of clonal sensitivity and targeted therapies, such as venetoclax in patients with t(11;14), require further study. Anti-plasma cell monoclonal antibodies, such as daratumumab, have been demonstrated to produce rapid responses with good tolerance, suggesting a role for this treatment early in the disease course but further studies are needed to evaluate its use in patients with advanced cardiac involvement.[9] Small molecules such as doxycycline or p38 MAP kinase inhibitors may help to reduce light chain cardiotoxicity. Immunotherapy agents such as NEOD001, a monoclonal antibody binding to an epitope unique to misfolded light chains, may accelerate cardiac amyloid fibril clearance and phase I data suggest the possibility of rapid cardiac responses.[10] Such agents may have a crucial role in early treatment with a dual mechanism.

In conclusion, treatment of advanced cardiac AL remains a major unmet medical need. While confirming the fragility and mortality of patients with this condition, our data shine a ray of hope that rapid responses with novel agent-based treatment can change outcomes even in this group of patients with very advanced disease. Larger international collaborative studies and novel imaging techniques may help to tease out factors influencing survival. Crucially, this study shows that this population of patients must be included in future prospective clinical trials of anti-amyloid and novel anti-plasma cell therapy.

Richa Manwani, Darren Foard, Shameem Mahmood, Sajitha Sachchithanantham, Thirusha Lane, Cristina Quarta, Taryn Youngstein, Tamer Rezk, Helen J Lachmann, Julian D. Gillmore, Marianna Fontana, Carol Whelan, Philip N. Hawkins and Ashutosh Wechalekar

National Amyloidosis Centre, University College London (Royal Free Campus), Rowland Hill Street, London, UK

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Correspondence: a.wechalekar@ucl.ac.uk

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