# Rapid hematological responses improve outcomes in patients with very advanced (Stage IIIb) cardiac immunoglobulin light chain amyloidosis

by 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 D. Wechalekar

# Rapid hematological responses improve outcomes in patients with very advanced (Stage IIIb) cardiac immunoglobulin light chain amyloidosis

Richa Manwani[1], Darren Foard[1], Shameem Mahmood[1], Sajitha Sachchithanantham[1], Thirusha Lane[1], Cristina Quarta[1], Taryn Youngstein[1], Tamer Rezk[1], Helen J Lachmann[1], Julian D Gillmore[1], Marianna Fontana[1], Carol Whelan[1], Philip N Hawkins[1] and Ashutosh D Wechalekar[1*]

[1] *National Amyloidosis Centre, University College London (Royal Free Campus), Rowland Hill Street, London*
* Corresponding Author:

Dr Ashutosh Wechalekar, National Amyloidosis Centre, University College London (Royal Free Campus), Rowland Hill Street, London, UK, NW3 2PF

Telephone number: +44 207 433 2733, Fax number: +44 207 433 2817
Email: a.wechalekar@ucl.ac.uk

Running head: Outcomes in advanced cardiac AL amyloidosis

Text word count: 1495

Number of figures: 1

Number of tables: 2

Number of references: 10

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 median overall survival (OS) in Stage I (NT-proBNP<332ng/L and Troponin-T<0.035µg/L), II (NT-proBNP>332ng/L or Troponin-T>0.035 µg/L) and III (NT-proBNP>332ng/L and Troponin-T>0.035µg/L) AL as 26.4, 10.5 and 3.5 months, respectively.[2] This has been refined, incorporating difference in involved and uninvolved serum free light chains (dFLC).[3] A European collaboration reported median OS 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>0.035µg/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. Modest improvement in outcomes in the latter study may be due to novel agent availability, 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 therefore report outcomes of 179 patients with Stage IIIb cardiac AL, showing that treatment responses can impact 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 (Troponin-T>0.035µg/L and NT-proBNP>8500ng/L) cardiac AL from 2009-2015 were included (n=179).  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, hematologic and amyloidotic organ responses were assessed according to amyloidosis consensus criteria.[6]  Primary outcome measures were OS and impact of hematologic response on survival.

179 patients were included.  Table 1 shows baseline characteristics.  Median age was 66.3 years (41.4-89.4 years).  44% had NYHA class 3-4 symptoms and 18% had ECOG score≥3. Median NT-proBNP was 14762ng/L (8500-147940ng/L).  Median LV wall thickness was 15mm (10-21mm); median LV ejection fraction (LVEF) was 49% (23-75%). 132 (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) 27%; cyclophosphamide, bortezomib and dexamethasone (CyBorD) 39%; bortezomib and dexamethasone 7%; melphalan and dexamethasone 2%; lenalidomide and dexamethasone 1%; other 7%.

On an intention-to-treat (ITT) basis (including all patients), 6 month hematologic responses were: complete response (CR) 35 (20%), very good partial response (VGPR) 25 (14%), partial response (PR) 32 (18%) and non-response 87 (48%) (including deaths prior to/after

treatment initiation). Thirty seven patients (21%) achieved CR/VGPR at Day 30. On an ITT basis, median OS was 6 months (Figure 1A). Patients in a CR/VGPR by Day 30 of treatment had median OS of 26 months, compared to 5 months in non-CR/VGPR (Figure 1C). Median OS in patients achieving 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 6 month CR/VGPR was 33% and 52% (p=0.04), respectively. There was a suggestion of better OS with CyBorD compared to CTD but the difference was not statistically significant (possibly due to small patient numbers and proportion of CTD patients also achieving a VGPR/better within one cycle) (Figure 1D).


Univariate and ROC analysis revealed that LVEF<55%, dFLC>400 mg/L and systolic blood pressure (SBP)<110 mmHg were predictors of poor survival. Median OS for patients with values above/below the threshold was: dFLC < vs. > 400 mg/L – 7 months vs. 3 months; LVEF > vs. < 55% - 10 months vs. 5 months; SBP > vs. < 110 mg Hg – 10 months vs. 5 months. In a multivariate model, not achieving a CR/VGPR at 6 months (HR 5.3, p<0.001; 95%CI 3.8-8.2), LVEF<55% (HR1.5 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 SBP<110mmHg (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 centre. That withstanding, median OS is 6 months, slightly better than survival previously described in 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 rapid response at Day 30 or overall CR/VGPR at 6 months had markedly better survival than ever reported in this patient cohort. 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 as a separate cohort[4] but patients are heterogeneous. Hypotension, poor systolic function and high presenting light chains (previously reported as poor prognostic factors in AL) were further determinants of survival. The European study reported lower hematologic responses (32% achieved ≥PR (ITT))[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% vs. 48% treated with a bortezomib-based regime, respectively). Hematologic responses to CyBorD in this cohort are similar to those in a previous multicentre 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 patient cohort, 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 by the 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 centre.

Although rapid hematologic response in one month improves survival, the challenge is to guide these fragile patients through chemotherapy, where 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 ITT and landmark analyses, we show that early response appears to translate into survival benefit at 12 months. However, hematologic response does not immediately impact upon 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 vs CTD, despite better hematologic responses in the CyBorD group. The small numbers limit utility of subset analysis but larger studies across international centres are planned to validate these results. Given the better early responses, bortezomib-based regimes would still be the 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 demonstrated rapid responses with good tolerance, suggesting a role for this 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 reduce light chain cardiotoxicity. Immunotherapy agents such as NEOD001, a monoclonal antibody binding to an epitope unique to misfolded light chains, may enable acceleration of cardiac amyloid fibril clearance and phase I data suggests 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. Whilst confirming the fragility and mortality of this population, these data shine a ray of hope that rapid responses with novel agent based treatment can change outcomes in even this very advanced patient group. Larger international collaborative studies and novel imaging may help to tease out factors impacting survival. Crucially, this study shows that this patient population must be included in future prospective clinical trials of anti-amyloid and novel anti-plasma cell therapy.

## References

1.      Merlini G, Seldin DC, Gertz MA. Amyloidosis: pathogenesis and new therapeutic options. J Clin Oncol. 2011;29(14):1924-1933.

2.      Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol. 2004;22(18):3751-3757.

3.      Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol. 2012;30(9):989-995.

4.      Wechalekar AD, Schonland SO, Kastritis E, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood. 2013;121(17):3420-3427.

5.      Wechalekar AD, Gillmore JD, Bird J, et al. Guidelines on the management of AL amyloidosis. Br J Haematol. 2015;168(2):186-206.

6.      Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia. 2012;26(11):2317-2325.

7.      Jaccard A, Comenzo RL, Hari P, et al. Efficacy of bortezomib, cyclophosphamide and dexamethasone in treatment-naive patients with high-risk cardiac AL amyloidosis (Mayo Clinic stage III). Haematologica. 2014;99(9):1479-1485.

8.      Merlini G, Lousada I, Ando Y, et al. Rationale, application and clinical qualification for NT-proBNP as a surrogate end point in pivotal clinical trials in patients with AL amyloidosis. Leukemia. 2016;30(10):1979-1986.

9.      Kaufman GP, Schrier SL, Lafayette RA, Arai S, Witteles RM, Liedtke M. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. Blood. 2017;130(7):900-902.

10.     Gertz MA, Landau HJ, Weiss BM. Organ response in patients with AL amyloidosis treated with NEOD001, an amyloid-directed monoclonal antibody. Am J Hematol. 2016;91(12):E506-e508.

**Table 1: Baseline characteristics.**

| n=179 | Median (range) | Frequency (%) |
|---|---|---|
| **General** | | |
| Median age (years) | 66.3 (41.4 –89.4) | |
| Male | | 102 (57%) |
| Female | | 77 (43%) |
| ECOG performance status<br>0<br>1<br>2<br>3<br>4 | | 0<br>29 (16%)<br>118 (66%)<br>32 (18%)<br>0 |
| Median 6-minute walk test (n=68, metres) | 184 (46-651) | |
| Involved light chain type<br>Kappa<br>Lambda | | 38 (21%)<br>141 (79%) |
| Median dFLC (mg/L) | 396 (0.7 - 12788) | |
| dFLC>400mg/L | | 87 (49%) |
| Median serum monoclonal paraprotein (g/L) | 5 (0 – 54) | |
| Serum paraprotein > 5g/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 (umol/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 (umol/L) | 10 (2-70) | |
| Median ALP (ULN 129 units/L) | 104 (35-1602) | |
| **Cardiac Parameters** | | |
| NYHA class<br>1-2<br>3-4<br>Not recorded | | 87 (49%)<br>67 (38%)<br>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 > 8500ng/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%) |

**Table 2: Hematologic responses by treatment.** (CTD: cyclophosphamide, thalidomide and dexamethasone; CyBorD: cyclophosphamide, bortezomib and dexamethasone).

| | n | Hematologic response at 30 days (ITT) | | | | | Hematologic response at 6 months (ITT) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 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%) |

**Figure 1. Overall survival of the entire cohort, by hematologic response and by treatment.**

a) 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 (which comprised 17% of the cohort) are included in this analysis. b) Median overall survival in those patients who achieved a CR (complete response)/VGPR (very good partial response), PR (partial response) or non-response (the latter including patients who died with and 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 achieved 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 in patients treated with bortezomib-based regimes and CTD.

A

Median survival 6 months

B

CR/VGPR - 38 months

PR - 7.4 months

NR - 2.6 months

Log rank p <0.0001

C

CR/VGPR at 30 days

<VGPR at 30 days

D

Bortezomib-based 8.9 months

CTD 7.2 months

Log rank p=0.438