Abnormal N-terminal fragment of brain natriuretic peptide in patients with light chain amyloidosis without cardiac involvement at presentation is a risk factor for development of cardiac amyloidosis

Primary light chain (AL) amyloidosis, the commonest type of amyloidosis, presents with cardiac involvement in 50% of patients. Cardiac amyloidosis causes a restrictive cardiomyopathy and is the major determinant of treatment related toxicity and death.[1] Echocardiography remains the gold standard for non-invasive patient assessment[2] although other techniques like cardiac MRI (CMR) scanning[3] appear to hold promise. N-terminal fragment of brain natriuretic peptide (NT-proBNP) is abnormal in cardiac amyloidosis[4] and high levels are associated with poor prognosis.[4,5] Early changes in NT-proBNP concentration occur after chemotherapy but the basis and significance remains unclear.[6] The significance of elevated NT-proBNP in the absence of cardiac involvement by the international consensus criteria (ICC)[7] has not been well studied.

We report significance of NT-proBNP in 102 patients with AL amyloidosis who did not have cardiac involvement by ICC amongst a stringently selected group of 169 patients with preserved renal function (creatinine clearance or eGFR >50 mL/min, <10% change in eGFR following treatment) who underwent assessment within protocols at the UK National Amyloidosis Centre (NAC) between 1999-2006, had a confirmed diagnosis of AL amyloidosis and had archived serum samples for retrospective analyses. NT-proBNP was measured using a Roche Elecsys 2010 analyzer and Roche Diagnostics assay kit. NT-proBNP cut off of 39 pMol/L (332 ng/L) was used based on previous reports.[5] This study was performed with informed consent from each patient in accordance with the Declaration of Helsinki, and received institutional review board approval.

The median age was 56 years (range 32-84) and a median number of 2 organs were involved: liver n=26 (16%), renal n=123 (73%), cardiac n=67 (40%). Median ECOG performance status was 2 (range 0-3). There was no significant difference in baseline characteristics between those with or without cardiac involvement. The median NT-proBNP for the whole cohort was 50 pMol/L (range 1-2525 pMol/L). NT-proBNP had a high degree of sensitivity for cardiac involvement (area under ROC curve 0.88, 95%CI 0.82-0.93). NT-ProBNP of 39 pMol/L had 89% sensitivity and 65% specificity for cardiac involvement (ICC[7] as gold standard) and had a significant impact on survival (P=0.003; *data not shown*).

One hundred and two of 169 (60%) patients had no evidence of cardiac involvement by ICC[7] and had median left ventricular wall thickness of 9 mm (7-11 mm). Forty of 102 (39%) had NT-proBNP of greater than 39 pMol/L with no significant difference in the baseline characteristics if NT-proBNP was equal to or less than or greater than 39 pMol/L, including response to chemotherapy (5 in each group did not respond (P=0.46)). NT-proBNP cut off 39 pMol/L remained prognostically significant in this subgroup and even lower NT-proBNP thresholds had prognostic significance; patients with NT-proBNP less than 15 pMol/L had better outcomes (HR 0.12; 95%CI 0.013-0.79; P=0.029) *versus* those with higher values with Kaplan-Meier estimated 5-year survival 98% *versus* 88%, respectively (Figure 1A; log rank P=0.007). On a median follow up of 60 months, 19 of 40 (47%) patients with NT-proBNP greater than 39 pMol/L at diagnosis had developed evidence of cardiac involvement by ICC compared to only 6 of 62 (10%) of those with NT-proBNP 39 pMol/L or below (relative risk 4.89; P<0.001) (Figure 1B).

After chemotherapy treatment using previously described regimes,[8-11] we confirmed earlier reports[6] of a significant decrease in NT-proBNP (median 444 to 144 pMol/L; P=0.021) among complete clonal responders, no significant change in partial responders, and a significant increase (from a median 53 pMol/L to 136 pMol/L; P<0.0001) in non-responders with no impact of NT-proBNP changes on survival in this stringently selected cohort. In summary, patients with AL amyloidosis who have modestly elevated NT-proBNP (>39 pMol/L) at presentation but no evidence of cardiac amyloidosis by

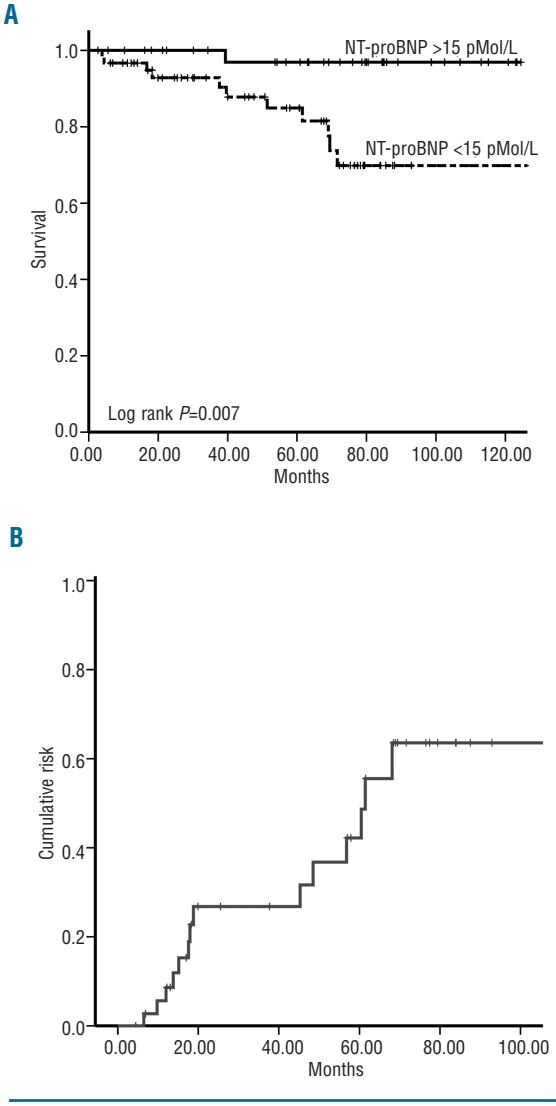

Figure 1. (A) Kaplan-Meier estimated overall survival for patients who did not have cardiac involvement by international consensus criteria (ICC) stratified by presenting NT-proBNP using a low threshold of 15 pMol/L. Patients with NT-proBNP over 15 pMol/L had worse outcomes even in the absence of cardiac involvement by ICC. (B) Kaplan-Meier estimated cumulative risk for development of cardiac amyloidosis by ICC in patients presenting with no evidence of cardiac amyloidosis but having presenting NT-proBNP over 39 pMol/L.

consensus criteria have a significantly higher risk (47% *vs.* 10% respectively; $P<0.001$) of developing cardiac amyloidosis than those with lower values (<39 pMol/L). Even subtle elevations of NT-proBNP (>15 pMol/L) have prognostic significance in patients without cardiac involvement by ICC, although the retrospective nature of this study limits identification of true causes of death. It appears likely that subtle elevation of NT-proBNP may predict existing cardiac amyloidosis which cannot be identified at echocardiography highlighting both the limitation of echocardiography and current consensus criteria for detecting early cardiac involvement. There is an urgent need to validate other tools, such as CMR and use of cardiac biomarkers, for early diagnosis of cardiac amyloidosis. These important observations need to be extended and confirmed in larger populations. Studies targeting this patient group with highly effective first-line treatments like bortezomib are needed to prove that cardiac amyloid progression can be prevented.

Ashutosh D. Wechalekar,[1] Julian D. Gillmore,[1] Nancy Wassef,[2] Helen J. Lachmann,[1] Carol Whelan,[1] and Philip N. Hawkins[1]

[1]National Amyloidosis Centre, University College London Medical School, London and [2]Dept. of Biochemistry, Royal Free Hospital, London, UK.

Correspondence: Ashutosh Wechalekar, National Amyloidosis Centre, Department of Medicine, University College London Medical School (Royal Free Campus), Rowland Hill St, London NW3 2PF, United Kingdom. Phone: international +44.20.74332758. Fax: international +44.20.74332817. E-mail: a.wechalekar@medsch.ucl.ac.uk

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