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LYMPHOID NEOPLASIA

Early cardiac response is possible in stage IIIb cardiac AL amyloidosis and is associated with prolonged survival

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KEY POINTS

- Early cardiac response is possible in patients with advanced cardiac AL amyloidosis.
- Graded cardiac response at 90 days predicts survival in stage IIIb AL amyloidosis.

Patients with immunoglobulin light chain (AL) amyloidosis and stage IIIb cardiac involvement have a dismal outcome despite the introduction of novel treatments. However, a rapid hematologic response translates in better survival. We evaluated the impact of early cardiac response and its depth on outcome in 249 patients with newly diagnosed stage IIIb cardiac AL amyloidosis. Hematologic and cardiac responses were evaluated by intent to treat. After a median follow-up of 52 months, 219 (84%) patients died, and median survival was 4.2 months. The 30- and 90-day hematologic response rates were 22% (at least very good partial response [VGPR] in 9%) and 24% (at least VGPR in 15%), respectively. Early hematologic response resulted in better survival. At 90 days, 21 (8%) patients achieved a cardiac response (cardiac very good partial response [cardiac VGPR] in 12 cases and cardiac partial response [cardiac PR] in 9). At the 90-day landmark analysis, cardiac response resulted in longer survival (median, 54 months), also in those patients who have achieved at least VGPR (median, 62 vs 26 months, $P = .011$). Patients with cardiac VGPR had a longer survival than those with cardiac PR (median, 92 vs 24 months; $P = .027$), whereas patients without cardiac response had a poor survival (median, 6 months). A baseline difference of involved/uninvolved free light chains > 50 mg/L (odds ratio [OR], 0.21, $P = .024$) and a bone marrow plasma cell infiltrate > 10% (OR, 0.23, $P = .040$) were negative predictors of 90-day cardiac response. Early cardiac responses are rare but possible in stage IIIb AL amyloidosis and translate to longer survival.

Introduction

Immunoglobulin light chain (AL) amyloidosis is caused by a usually small B-cell clone that synthesizes misfolded light chains that deposit in tissues and organs as insoluble amyloid fibrils. Cardiac involvement is present in almost 80% of cases, and it is the most prominent driver of prognosis.[1] Severity of heart involvement is accurately evaluated by staging systems based on N-terminal natriuretic propeptide type-B (NT-proBNP) and cardiac troponins.[2-4] The European staging system identifies stage IIIb patients as those with the most severe cardiac amyloidosis and poor survival.[4,5] Recent data indicates that the outcome of these patients did not improve in recent years, despite the introduction of novel and effective treatments.[6] There is the hope that daratumumab combinations, recently approved as standard of care in stage I-IIIa patients, may favorably impact the outcome of subjects with very advanced cardiac involvement, and a phase II study of daratumumab single agent (#NCT04131309; clinicaltrials.gov) is underway. Preliminary results were encouraging.[7]

The International Society of Amyloidosis defines hematologic and cardiac response based on changes in circulating free light chains, on immunofixation of serum and urine,[8,9] and on changes in NT-proBNP, respectively.[8] Hematologic and cardiac response can be combined to assess whether the treatment induced a satisfactory response.[10] Although hematologic response is graded, the possibility of grading cardiac response has been proposed[11] and is being validated in a large international study.[12] Achieving an early hematologic response (within 30 days from treatment initiation) is important in AL amyloidosis, and it is associated with longer survival and higher rates of organ responses.[13] This is even more crucial in stage IIIb patients. The National Amyloid Center group of London, United Kingdom, suggested to evaluate hematologic response 30 days after starting chemotherapy and base the decision on the subsequent therapeutic strategy on this assessment.[14] However, the possibility to achieve an early cardiac response in stage IIIb patients and its impact on outcome has not been evaluated yet.

In this study, we present a large series of 249 patients with newly diagnosed stage IIIb AL amyloidosis from a prospectively maintained database, we explore factors able to further stratify outcomes in this subgroup, and we evaluate the impact of early cardiac response and progression on overall survival (OS). We

Table 1. Characteristics of 249 patients with stage IIIb AL amyloidosis

Variables	Overall population 249 patients N (%), mean (IQR)
Age, years	68 (60-74)
Sex, male	145 (58)
Organ involvement (other than heart)	
Kidney	129 (52)
Liver	43 (17)
ST	51 (20)
GI	6 (2)
ANS	21 (8)
PNS	23 (9)
Number of involved organs	2 (1-3)
Isolated heart involvement	74 (30)
NYHA class	
I	33 (13)
II	64 (26)
III	139 (56)
IV	13 (5)
NT-proBNP, ng/L	17089 (12179-25014)
Troponin I, ng/mL	0.265 (0.169-0.500)
eGFR, mL/min × 1.73 m^2	43 (27->60)
eGFR < 30 mL/min × 1.73 m^2	76 (31)
Renal stage	
I	108 (43)
II	111 (45)
III	26 (10)
Patients in dialysis at diagnosis	2 (1)
dFLC, mg/L	259 (142-543)
dFLC < 50 mg/L	13 (5)
dFLC > 180 mg/L	167 (67)
Involved/uninvolved FLC rate > 100	9 (4)
BMPC, %	12 (8-20)
BMPC > 20%	41 (16)
Treatment	
MDex	98 (39)
CyBorD	75 (30)
BMDex	43 (18)
IMiDs	28 (11)
rituximab	5 (1)

ANS, autonomic nervous system involvement; BMDex, bortezomib, melphalan, and dexamethasone; BMPC, bone marrow plasma cells; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; FLC, free light chain; GI, gastrointestinal; IMiDs, immunomodulatory drugs; IQR, interquartile range; PNS, peripheral nervous system; ST, soft tissues.

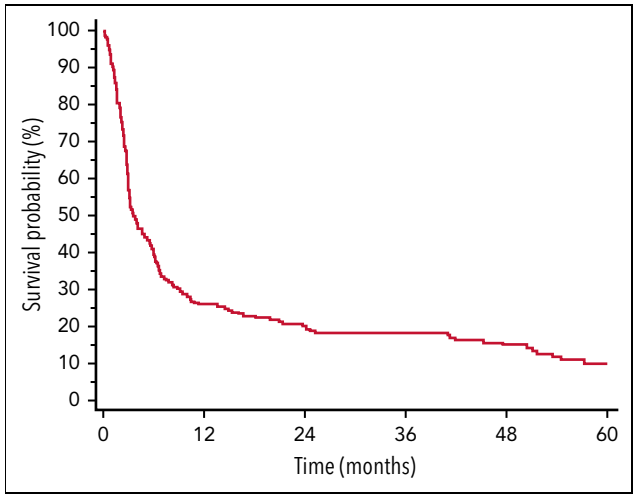

Figure 1. OS in 249 patients with stage IIIb AL amyloidosis.

also assessed the applicability of the recently proposed graded cardiac response criteria and combined hematologic and organ response criteria in this setting.[10-12]

Methods

The prospectively maintained database of 1378 patients with AL amyloidosis newly diagnosed at the Amyloid Research and Treatment Center in Pavia between 2004 and 2018 was searched for stage IIIb cases according to the European staging system. Two hundred forty-nine consecutive patients were included in the study. The study was approved by the ethics committee, and all subjects gave written informed consent for their clinical data to be used for research purposes, in accordance with the Declaration of Helsinki.

Cardiac stage IIIb was defined as NT-proBNP > 8500 ng/L and troponin I > 0.100 ng/mL at diagnosis according to the European staging system.[4] The method for measurement of troponin I was changed in November 2018 to an ultrasensitive assay. Troponin I was then remeasured with the new assay on the frozen serum samples stored in our biobank in all patients who were evaluated at our center before November 2018 for consistency.

Diagnosis of AL amyloidosis was established after histological identification and accurate typing of amyloid deposits on tissue biopsies with immunoelectron microscopy or mass spectrometry.[15-17] Organ involvement was defined as per consensus criteria.[18] The severity of renal involvement was assessed by the validated renal staging system with 24-hour proteinuria and estimated glomerular filtration rate (eGFR).[19]

All the patients were evaluated by an expert cardiologist at the first evaluation at our center. During the cardiologic evaluation, heart failure treatment with diuretics was reviewed in all cases and optimized when needed before starting chemotherapy for AL amyloidosis. The New York Heart Association (NYHA) class was assessed both by the amyloid center cardiologist and the physician coordinating the patient's evaluation. Assessment of NYHA class was concordant in all patients.

Table 2. Univariable and multivariable analysis for survival in patients with stage IIIb amyloidosis

Univariable analysis (249 patients)			
Variables	**Hazard ratio**	**95% CI**	***P***
Sex, male	1.22	0.96-1.67	0.158
NYHA class I	0.57	0.37-0.89	0.014
Troponin I > 0.500 ng/mL	1.50	1.10-2.50	0.010
NT-proBNP(ln), ng/L	1.53	0.81-2.87	0.186
eGFR < 30 mL/min × 1.73 m^2	0.71	0.52-0.96	0.028
LC isotype κ vs λ	1.18	0.84-1.66	0.326
dFLC > 50 mg/L	0.53	0.26-1.09	0.083
dFLC > 180 mg/L	1.17	0.87-1.56	0.296
dFLC > 500 mg/L	1.94	1.43-2.63	<0.001
BMPC > 20%	1.03	0.65-1.63	0.888
Bortezomib-based treatment, yes	0.85	0.65-1.12	0.254
Treatment with CyBorD, yes	0.81	0.59-1.11	0.192
Treatment with BMDex, yes	1.22	0.85-1.74	0.274
Treatment with MDex, yes	1.02	0.77-1.35	0.906
Multivariable analysis (173 patients with eGFR > 30 mL/min × 1.73 m^2)			
NYHA class I	0.80	0.48-1.33	0.392
Troponin I > 0.500 ng/mL	1.22	0.81-1.83	0.340
dFLC > 500 mg/L	1.83	1.28-2.62	0.001

BMDex, bortezomib, melphalan, and dexamethasone; CI, confidence interval; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; LC, light chains.

The treatment strategy was protocolized. Briefly, upfront bortezomib was not available before 2010, and patients were treated with oral melphalan dexamethasone (MDex) or immune modulatory drugs according to age (above or below 65 years) and eGFR (above or below 30 mL/min) to avoid oral melphalan in younger subjects and in those with renal failure. After 2010, bortezomib combinations (with melphalan or cyclophosphamide according to age and eGFR)[5,20] were preferred, but MDex was still offered to subjects with contraindications to bortezomib (peripheral neuropathy or lung disease) and to those who preferred an oral treatment. Patients with immunoglobulin M expressing clones received rituximab-based therapy. All regimens were attenuated. Daily dexamethasone dose did not exceed 20 mg, and bortezomib was started at 0.7 or 1.0 mg/m^2 and escalated to 1.3 according to tolerability.[21-23]

Hematologic response was evaluated by intent to treat at 30 and 90 days from the day of starting chemotherapy and was assessed according to current validated criteria.[8,9] Patients with a baseline difference between involved and uninvolved free light chains (dFLC) between 50 mg/L and 20 mg/L were evaluable with the low-dFLC criteria.[24-28] Cardiac response, defined as a decrease of NT-proBNP > 300 ng/L and >30% from baseline,[8] was evaluated by intent to treat after 90 days from starting treatment. Cardiac response was graded according to the recently proposed criteria for graded organ response: complete cardiac response (cardiac CR) if NT-proBNP was < 400 ng/L; very good partial cardiac response (cardiac VGPR) in the presence of a reduction of NT-proBNP > 60% and not meeting the cardiac CR definition; and partial cardiac response (cardiac PR) if NT-proBNP decrease was between 60% and 30%.[11] A combined hematologic and cardiac and hematologic response (CHCR) model was tested for the identification of subjects with better outcome after treatment. CHCR was built referring to the proposed and validated combined hematologic and organ response model.[10] More precisely, it was designed using combining scores of 0 to 3 for hematologic response (0, complete response [CR]; 1, very good partial response [VGPR]; 2, partial response [PR]; 3, no response [NR]) and 0 to 1 for cardiac response (0, cardiac response; 1, no cardiac response).

Fisher's exact test and Mann-Whitney *U* test were used to assess differences in nominal and continuous variables between groups as appropriate. Median and interquartile range were reported for continuous variables. Survival was

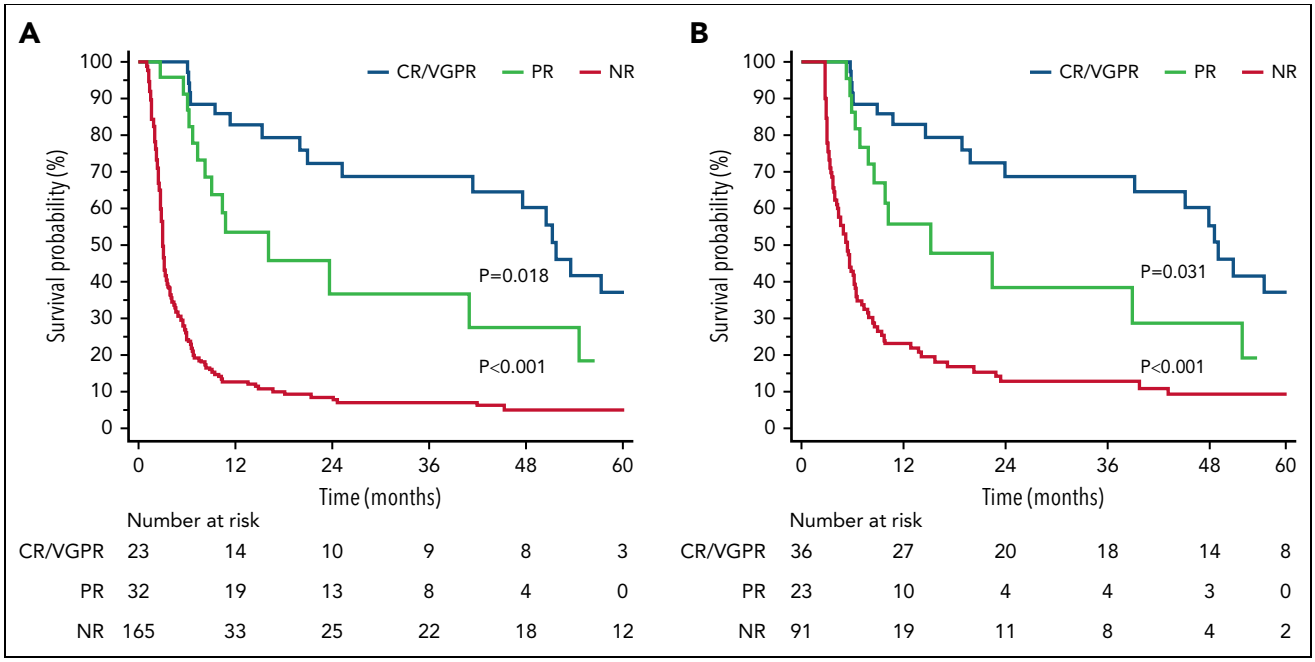

Figure 2. Hematologic response at 30 and 90 days in stage IIIb AL amyloidosis. Survival according to the depth and quality of hematologic response at 30 days from treatment initiation: CR/VGPR median survival, 52 months; PR median survival, 16 months; and NR median survival, 3 months. (A) Survival according to the depth and quality of hematologic response at 90 days from treatment initiation: CR/VGPR median survival, 52 months; PR median survival, 16 months; and NR median survival, 6 months. (B) A 30- and 90-day landmark analysis was performed.

calculated from diagnosis to death or last contact. Survival curves were plotted according to Kaplan-Meier, and differences in OS were tested for significance with the log-rank test. A 30- and 90-day landmark analysis was performed to evaluate the impact of hematologic and cardiac response at specific time points. Cox hazard regression models and logistic regression analysis was performed to identify factors predicting survival and cardiac response, respectively. Receiver-operating characteristic analyses based on death at 3 months were used to identify dFLC and troponin I cutoffs best discriminating survival. MedCalc Statistical Software version 14.12.0 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014) was used for computation.

Results

Patient characteristics are reported in Table 1. Of the 249 patients with stage IIIb AL amyloidosis, 74 (30%) had isolated heart involvement. Clone-related prognostic factors, namely dFLC > 180 mg/L and bone marrow plasma cellular infiltrate > 20%, were present in 67% and 16% of patients, respectively. Remarkably, a small but not negligible number were in NYHA class I (13% of cases). Patients received a bortezomib-based regimen in 118 (47%) cases. Of the 165 patients diagnosed between 2010 and 2018, 111 (67%) received bortezomib. Oral MDex was the most frequent treatment in patients who were not exposed to bortezomib.

We compared baseline variables in NYHA class I patients and in the other stage IIIb patients (supplemental Table 1, available on the *Blood* Web site). The only significant difference was the concentration of troponin I (median, 0.196 vs 0.289 ng/mL, $P = .017$).

After a median follow-up of living patients of 52 months, 219 (84%) patients died, and median OS was 4.2 months. The cumulative proportion surviving was 91% at 1 month, 61% at 3 months, 41% at 6 months, and 26% at 12 months (Figure 1).

Results of the univariable analysis for factors predicting OS are reported in Table 2. This analysis revealed that dFLC > 500 mg/L (hazard ratio [HR], 1.94; 95% CI, 1.43-2.63; $P < .001$) and troponin > 0.500 ng/mL (HR, 1.50; 95% CI, 1.10-2.50; $P = .010$) were associated with worse survival, whereas having a NYHA class I at diagnosis resulted in better outcome (HR, 0.57; 95% CI, 0.37-0.89; $P < .014$). Treatment regimens (considered as single regimens and as bortezomib-based vs non–bortezomib-based) were not associated with survival. We observed that reduced eGFR (<30 mL/min × 1.73 m^2) was a protective factor (HR, 0.71; 95% CI, 0.52-0.96; $P = .028$). Due to the possible interference of reduced glomerular filtration on NT-proBNP concentration and staging, we elected to exclude from the multivariable analysis patients whose eGFR was <30 mL/min × 1.73 m^2 (Table 2). On multivariable analysis, dFLC > 500 mg/L emerged as the only independent prognostic factor for survival at diagnosis (HR, 1.83; 95% CI, 1.28-2.62; $P = .001$). Overall, 69 (28%) patients had a dFLC level > 500 mg/L, and their median OS was 2.7 months. In 7 cases (10%), the involved/uninvolved free light chain ratio was >100.

A hematologic response was observed in 55 (22%) patients (CR, 3%; VGPR, 6%; PR, 13%) at 30 days from treatment initiation and in 59 (24%; CR, 5%; VGPR, 10%; PR, 9%) at 90 days. The presence and depth of hematologic response were significantly associated with OS at both day 30 and day 90 (Figure 2A-B). The benefit of a hematologic response on

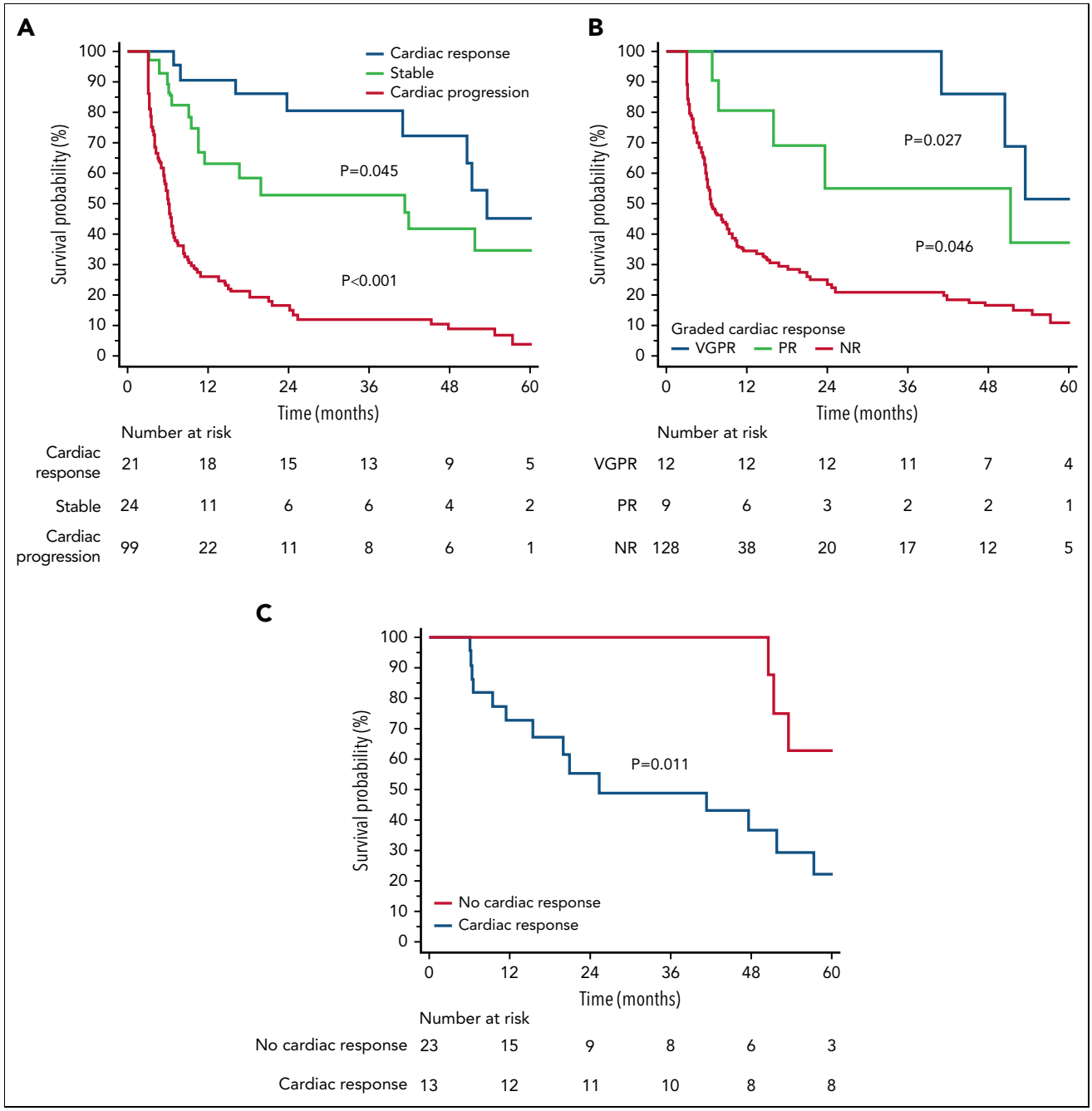

Figure 3. Early cardiac response (90 days) in stage IIIb AL amyloidosis. Survival in patients with a cardiac response (median survival, 54 months), cardiac stable disease (median survival, 20 months), or cardiac progression (median survival, 6 months). (A) Survival according to depth of cardiac response: cardiac VGPR (median survival, 92 months), cardiac PR (median survival, 24 months), and cardiac NR (median survival, 6 months). (B) Survival according cardiac response in patients who attained a profound hematologic response (ie, at least VGPR). (C) Ninety-day landmark analysis was performed.

survival was observed both in patients treated with bortezomib and in those exposed to MDex (supplemental Figure 1).

At 90 days, cardiac response was achieved in 21 (8%) cases, of which 12 obtained a cardiac VGPR and 9 a cardiac PR. None achieved a cardiac CR. Increase of diuretic usage within 90 days from diagnosis was observed in none of the patients who achieved a cardiac response. On the contrary, 20% of cardiac responders and 5% of those with no cardiac response had a reduction in diuretic usage, although this difference was not statistically significant ($P = .097$). In 204 (82%) patients, a cardiac progression was observed, whereas 24 (10%) were classified as stable. The 90-day landmark analysis showed that patients with a cardiac response had a longer OS (median 54 months) than those with stable cardiac disease (median 20 months) or cardiac progression (median 6 months; Figure 3A). Moreover, the deeper the cardiac response, the better was the benefit in survival (cardiac VGPR median survival, 92 months; cardiac PR median survival, 24 months; cardiac NR median survival, 6 months; Figure 3B). The presence of cardiac response resulted in better survival also in the subgroup of patients with dFLC > 500 mg/L at diagnosis (median survival, 41 vs 4 months,

Table 3. Univariable logistic regression for predictors of cardiac response at 90 days

Variables	Odds ratio	95% CI	*P*
Sex, male	0.64	0.25-1.62	0.349
NYHA class I	1.13	0.35-3.70	0.835
Troponin I > 0.500 ng/mL	1.02	0.31-3.30	0.974
eGFR < 30 mL/min × 1.73 m^2	0.90	0.32-2.54	0.845
LC isotype κ vs λ	0.53	0.20-1.46	0.221
dFLC > 50 mg/L	0.21	0.05-0.82	0.024
dFLC > 180 mg/L	0.56	0.22-1.41	0.217
dFLC > 500 mg/L	0.97	0.30-3.13	0.959
BMPC > 10%	0.23	0.06-0.94	0.040
Bortezomib-based treatment, yes	1.13	0.45-2.86	0.788
Treatment with CyBorD, yes	1.18	0.44-3.16	0.736
Treatment with BMDex, yes	0.90	0.24-3.34	0.875
Treatment with MDex, yes	0.96	0.37-2.48	0.933

BMDex, bortezomib, melphalan, and dexamethasone; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; LC, light chains.

P = .015; supplemental Figure 2) and in those who achieved a CR/VGPR at 90 days (median survival, 62 vs 26 months, *P* = .011; Figure 3C).

A CHCR model was built to evaluate the impact of the combination of hematologic response and cardiac response on survival after 90 days from treatment initiation. At this timepoint, CHCR score was 0 to 2 in 39 (16%) and 3 to 4 in 210 (84%) cases. At the 90-day landmark analysis, patients with a CHCR score of 0 to 2 had a significantly longer OS (median, 51 vs 6 months; *P* < .001; Figure 4). None of the patients who achieved a cardiac response had less than a hematologic PR, and only 3 of them achieved less than a VGPR.

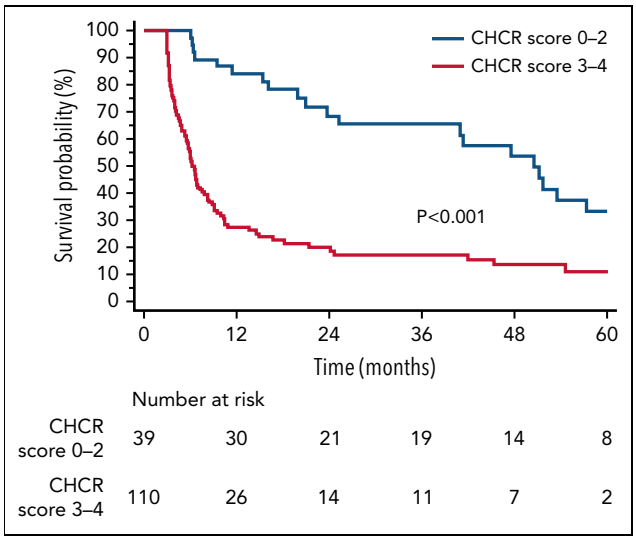

Figure 4. A composite hematologic and cardiac response at 90 days in stage IIIb AL amyloidosis. Differences in survival among patients with a CHCR score of 0 to 2 and 3 to 4 after 90 days from treatment initiation. A 90-day landmark analysis was performed.

Finally, we searched for predictors of cardiac response at 90 days (Table 3). At univariable logistic regression analysis, having a dFLC > 50 mg/L (OR, 0.21; 95% CI, 0.05-0.82; *P* = .024) and BMPC > 10% (OR, 0.23; 95% CI, 0.06-0.94; *P* = .040) at diagnosis was associated with a lower probability of reaching cardiac response. Type of treatment did not emerge as a predictor of cardiac response.

Discussion

This is the largest study on stage IIIb AL amyloidosis published so far and the first specifically addressing cardiac response in stage IIIb AL amyloidosis and showing that early NT-proBNP improvements are associated with improved outcomes in patients with very advanced AL amyloidosis, including those who attain deep hematologic response.

As previously reported, the outcome of stage IIIb patients was extremely poor also in our series, with a median survival of only 4.2 months and 74% of patients dying within 1 year from diagnosis.[14,29] A nonnegligible proportion (13%) of patients in this series collected with a protocolized assessment of signs and symptoms at baseline were classified as NYHA class I. However, this did not have an independent impact on survival, and the only variable independently predicting the outcome of stage IIIb patients was a high (>500 mg/L) dFLC level.

Somewhat surprisingly, a severe reduction of eGFR (<30 mL/min) was associated with better survival. We interpreted this observation as an effect of severely reduced glomerular

filtration on the clearance of NT-proBNP, which might have led to classifying as stage IIIb some patients with relatively less advanced heart involvement. Dittrich et al explored the impact of low eGFR (<50 mL/min) on the performance of the staging systems in AL amyloidosis and found that reduced glomerular filtration was an independent predictor of poorer outcome.[30] We had previously shown that in patients with end-stage renal failure (eGFR < 15 mL/min), BNP was a better predictor of survival than NT-proBNP.[31] Based on the results of Dittrich et al, we advocated further studies on the impact of severely reduced eGFR on staging.[32] The present observation further emphasizes the need for larger studies addressing the impact of reduced glomerular filtration as a possible independent prognostic factor, as well as a variable interfering with cardiac staging in AL amyloidosis. This could allow refinements in staging and in eligibility criteria for clinical trials.

In the present study, early (90 days after treatment initiation) NT-proBNP response was unfortunately rare (8%). Nevertheless, cardiac response was able to significantly improve OS even in stage IIIb subjects. Not only was cardiac response possible at this early assessment after treatment initiation, but it could also be graded according to the recent proposal by the Mayo Clinic group,[11,12] and deeper cardiac response was associated with a more pronounced improvement of survival.

As previously reported by Manwani et al,[14] hematologic response at 30 and 90 days also predicted survival in this group. In the present series, the 30-day rate of CR/VGPR was lower than that reported by the London group (9% vs 21%), but OS seemed to be better (52 vs 26 months). The proportion of patients treated with a bortzomib-based regimen was similar (48% vs 46%), and it is possible that other factors explain the lower CR/VGPR rate in our study. For instance, a higher proportion of patients in our series were NYHA class III/IV (61% vs 38%).

Remarkably, cardiac response further prolonged OS also in subjects who attained a deep hematologic response (at least VGPR), indicating that both hematologic and cardiac response can be used in early assessment of treatment efficacy also in this population of patients with very advanced heart involvement. Indeed, the recently proposed criteria for combined hematologic and organ response assessment provided a sharp discrimination of outcome in our series. Interestingly, when we analyzed possible predictors of irreversible cardiac dysfunction, we found that a relatively low dFLC value (>50 mg/L) made cardiac response less likely. However, cardiac response improved survival also in patients with high dFLC. Overall, these observations corroborate the link between cardiac dysfunction and circulating free light chains in AL amyloidosis that was supported by previous in vitro and in vivo studies.[33-35]

As previously reported,[6] the type of treatment did not have an impact on OS. However, our study was not designed to assess a treatment effect on survival, because treatment allocation was influenced by variables with a prognostic impact (age and eGFR). Nevertheless, we confirmed the data reported by Vaxman et al[29] that bortezomib-based treatment does not seem to have an impact on the proportion of patients dying within the first 12 months from diagnosis. Yet, it is clear that improvement of treatment of stage IIIb AL amyloidosis is urgently needed. Hopefully, the introduction of novel and rapidly acting drugs such as daratumumab may change the clinical history also of these patients.[36]

We recognize that, despite the large number of patients included in the study, a possible limitation is the low number of hematologic and cardiac responses. Given the rarity of the disease and the peculiar frailty of patients with stage IIIb AL amyloidosis, only large international cooperative studies can further address the impact of cardiac response in these subjects with advanced cardiac disease.

In conclusion, our study shows that cardiac dysfunction can be rapidly reversible in patients with stage IIIb AL amyloidosis. These patients should be treated with delicate and rapidly acting regimens to induce profound reductions of the amyloid light chain. Hopefully, the proportion of patients in whom this result is obtained will improve with the recent introduction of more effective anti–plasma cell agents[7] and by immunotherapy targeting the amyloid deposits.[37,38] Early assessment and grading of cardiac response is a useful complement to assessment of hematologic response in stage IIIb patients and may be used to guide therapeutic decisions.

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Authorship

Contribution: M.B. designed the study, wrote the manuscript, collected and analyzed data, and evaluated patients; P.M. designed the study, collected data, and evaluated patients; G.P. designed the study, wrote the manuscript, and evaluated patients; A.F., M. Nuvolone, P.B., M. Nanci, F.F., and C.B. evaluated patients; and G.M. evaluated patients, critically reviewed the manuscript, and gave final approval.

Conflict-of-interest disclosure: M.B. reports honoraria for lectures from Jannsen. P.M. reports honoraria for lectures from Pfizer and Jannsen-Cilag and travel support from Celgene. M. Nuvolone reports honoraria for lectures from Jannsen. A.F. reports honoraria for lectures from Jannsen. G.P. reports advisory board membership and honoraria from Janssen, Protego, and Zentalis; and honoraria from Pfizer, Sebia, Siemens, and The Binding Site. The remaining authors declare no competing financial interests.

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Footnotes

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For original data, please contact giovanni.palladini@unipv.it.

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