Outcome of Cardiac Light-Chain Amyloidosis in the Era of Novel Therapy
— A Single-Center Cohort Study of 227 Patients —

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Background: Cardiac involvement occurs in more than half of the patients with light-chain amyloidosis (AL), but the characteristics, treatment and prognosis of cardiac AL (CAL) are not fully described.

Methods and Results: A total of 227 patients with CAL diagnosis between January 2009 and March 2017 at Peking Union Medical College Hospital were included. Patients with Mayo stages I, II and III AL accounted for 0.9%, 49.8% and 49.3%, respectively. Autologous stem cell transplantation, bortezomib combinations, non-bortezomib regimens and palliative treatment were given as first line therapy in 3.1%, 44.1%, 30.8% and 22.0% of patients, respectively. Overall hematological response and cardiac response were achieved in 60.6% and 37.2% of evaluable patients, respectively. The median overall survival (OS) was 17 months in all patients, and 10 months in those with Mayo stage III. In patients with Mayo stage III disease who survived for >1 month, the bortezomib group survived significantly longer than the non-bortezomib group (median OS, not reached vs. 12 months, P=0.019). Three independent prognostic factors for survival were identified: N-terminal fragment of B-type natriuretic peptide (NT-proBNP) ≥5,000 pg/mL, bone marrow plasma cells ≥10%, and systolic blood pressure <100 mmHg.

Conclusions: CAL patients had poor prognosis, but those treated with bortezomib combinations had a better outcome than the non-bortezomib group.

Key Words: Bortezomib; Cardiac amyloidosis; Light-chain amyloidosis; NT-proBNP

Light-chain amyloidosis (AL) is a rare systemic disorder caused by the deposition of misfolded amyloid fibrils derived from the monoclonal immunoglobulin light-chain in organs. Cardiac involvement occurs in more than half of patients at diagnosis of AL and is a major determinant of the treatment options and prognosis. Cardiac AL (CAL) patients have a poor prognosis and the median survival without treatment is approximately 6 months. In recent years, overall survival (OS) has been improved by high-dose melphalan followed by autologous stem cell transplantation (HDM/ASCT) for selected patients and/or combination chemotherapy with novel antiplasma cell agents such as bortezomib however, the median survival of patients with Mayo stage III CAL remains as short as 7 months. Therefore, early recognition and appropriate treatment are necessary to improve long-term survival. In this study, we describe the clinical features, treatment, and outcomes of a large cohort of Chinese CAL patients, and explore the risk factors associated with survival.

Methods

Patients
Medical records were reviewed to identify patients who had a discharge diagnosis of AL between January 2009 and March 2017 at Peking Union Medical College Hospital. The definition of AL and assessment of organ involvement were based on the consensus criteria published in 2005 and modified in 2012. AL was biopsy-proven by Congo red staining, and the deposits were characterized as AL type by immunohistochemistry, immunofluorescence, or laser microdissection with mass-spectrometry-based proteomic analysis. Myeloma was carefully ruled out by special
Treatment Regimens used for treatment included HDM/ASCT, bortezomib-containing regimens, regimens without bortezomib (including melphalan-dexamethasone, alkylating agent-thalidomide-dexamethasone combination, and lenalidomide combinations), and palliative treatment. Patients who met the criteria were candidates for HDM/ASCT: physiologic age ≤ 70 years; blood pressure ≥ 90 mmHg; estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m²; ECOG performance status ≤ 2; Mayo stage I or II; NYHA functional status Class I or II; ejection fraction >55%; no severe pleural effusions. Therapeutic decisions were made based on the physician’s advice and the patient’s wishes.

Hematological and organ responses were assessed according to the Consensus Opinion from the 10th International Symposium on Amyloid and Amyloidosis. A hematological very good partial response (VGPR) was defined as the difference between involved and uninvolved serum free light-chain concentration (dFLC) <40 mg/L. Survival was calculated from the date of diagnosis until the date of last follow-up, or death. Early death was defined as death within 3 months after diagnosis. The primary outcome measure was OS and the effect of a hematological response to treatment on survival.

Ethical Statement
This study was approved by the Clinical Research Ethics Committee of Peking Union Medical Center Hospital, Beijing, China. Because of the study’s retrospective nature, written informed consent by patients was waived by the Committee.

Table 1. Baseline and Clinical Characteristics of AL Patients With and Without Cardiac Involvement

| Characteristic | CAL (n=227) | Non-CAL (n=105) | P value |
|---------------|-------------|-----------------|---------|
| Age, years    | 57.0 (37–81) | 58.0 (20–84)    | 0.851   |
| Male sex      | 151 (66.5%)  | 64 (61.0%)      | 0.323   |
| Symptoms to diagnosis, months | 12.0 (1–104) | 8.0 (1–432) | 0.077   |
| M protein     | 59 (26.0%)   | 38 (36.2%)      | 0.507   |
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| dFLC, mg/L (n=182) | 200.6 (1.6–4,263.0) | 51.0 (0.6–1,575.3) | <0.001 |
| Bone marrow ≥10% plasma cells | 33/198 (16.7%) | 6/94 (6.4%) | 0.016   |
| Organ involvement |             |                 |         |
| Renal involvement | 153 (67.4%) | 83 (79.0%) | 0.030   |
| PN             | 52 (22.9%)   | 7 (6.7%)        | <0.001  |
| Liver          | 49 (21.6%)   | 25 (23.8%)      | 0.651   |
| Gastrointestinal | 29 (12.8%) | 5 (4.8%)       | 0.025   |
| Involved organs ≥3 | 85 (37.4%) | 6 (5.7%)       | <0.001  |
| Biomarkers     |             |                 |         |
| 24-h urine protein, g | 1.5 (0.0–25.0) | 4.6 (0.06–34.0) | <0.001 |
| eGFR, mL/min/1.73 m² | 83.0 (6.0–136.0) | 88.1 (9.3–177.0) | 0.304 |
| Serum albumin, g/L | 33.0 (13.0–53.0) | 30.0 (11.0–50.0) | 0.005 |
| ALP, g/L       | 89.0 (30.0–919.0) | 76.0 (25.0–1,546.0) | 0.264 |

AL, light-chain amyloidosis; ALP, alkaline phosphatase; CAL, AL with cardiac involvement; dFLC, difference between involved and uninvolved serum free light-chain concentration; eGFR, estimated glomerular filtration rate; PN, peripheral neuropathy.

Baseline Evaluation and Follow-up
Patients’ work-up included clinical evaluation and a complete laboratory assessment (full blood count, basic biochemistry, protein analysis with serum and urine immunofixation and electrophoresis, and serum immunoglobulin free light-chains). Bone marrow aspirate and biopsy data were also obtained.

Cardiac evaluation at baseline and during follow-up included a complete physical examination, 12-lead ECG, echocardiography, magnetic resonance imaging (MRI) and assessment of cardiac biomarkers. NT-proBNP and cardiac troponin I (cTnI) levels were measured with standard commercially available assays. Cardiac function was evaluated using the New York Heart Association (NYHA) classification.

Disease Stage
The Mayo stage criteria were used for stratification. Patients were classified as having stage I, II or III disease based on whether they had none, one or both of the following findings: NT-proBNP ≥332 ng/L and cTnI ≥0.1 ng/mL. Furthermore, stage III patients were divided into stage IIIa or stage IIIb based on whether NT-proBNP was below or above 8,500 ng/L.

Organ damage (anemia, hypercalcemia, renal failure, and bone lesion) caused by myeloma, especially in patients with ≥10% plasma cells in the bone marrow. Cardiac involvement was defined as mean left ventricular wall thickness on echocardiography >12 mm in the absence of hypertension or other potential causes of left ventricular hypertrophy, or N-terminal fragment of B-type natriuretic peptide (NT-proBNP) >332 ng/L in the absence of renal failure or atrial fibrillation. Only patients with CAL were included in this study and compared with AL patients without cardiac involvement.

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AL, light-chain amyloidosis; ALP, alkaline phosphatase; CAL, AL with cardiac involvement; dFLC, difference between involved and uninvolved serum free light-chain concentration; eGFR, estimated glomerular filtration rate; PN, peripheral neuropathy.
Cardiac AL-Amyloidosis

with AL; of them, 227 (68.4%) had cardiac AL and 105 did not. The demographic and clinical characteristics of both groups are compared in Table 1. CAL patients had a higher median serum dFLC concentration, and more patients had bone marrow plasma cells ≥10%. CAL patients had more gastrointestinal and peripheral neuropathic involvement but less renal involvement. More than one-third of CAL patients had ≥3 organs involved, which was more than in the non-CAL patients. When biomarkers were evaluated, CAL patients had a lower median level of 24-h urine protein, but a higher median level of serum albumin.

Cardiac parameters in CAL patients are listed in Table 2. About half of them were in NYHA Class III or IV and had SBP <100 mmHg. The median value of the different cardiac biomarkers was 4,566 ng/L (range, 222–103,277) for NT-proBNP and 0.10 ng/mL (range, 0–16.5) for cTnI; 103 patients (47.2%) and 66 patients (30.3%) had NT-proBNP ≥5,000 ng/L and 8,500 ng/L, respectively. Among all the data are expressed as percentages and were compared using the chi-square or Fisher’s exact test. Mean and standard deviation are presented for normally distributed variables and median and range for non-normally distributed ones. All P values were two-sided with a significance level of 0.05. Receiver-operating characteristic (ROC) analysis with death at 1 year was used to identify the threshold for NT-proBNP, cTnI, left ventricular ejection fraction (LVEF), systolic blood pressure (SBP), and dFLC, which were then analyzed as dichotomous variables. Survival was assessed by the Kaplan-Meier method and compared by log-rank test. Cox multivariable regression models were fitted, including non-collinear predictive variables. Patients who died prior to response assessment were classified as non-responders.

Table 2. Cardiac Parameters in Patients With CAL

| Parameter                  | Median (range) or no. of patients (%) | P value |
|----------------------------|--------------------------------------|---------|
| NYHA grade III–IV          |                                      |         |
| Cardiac AL (n=227)         | 107 (48.9%)                          | <0.001  |
| Non-CAL (n=105)            | 0                                    |         |
| SBP, mmHg                  |                                      |         |
| Cardiac AL (n=227)         | 100 (55–160)                         | <0.001  |
| Non-CAL (n=105)            | 118 (78–170)                         |         |
| cTnI, ng/mL                |                                      |         |
| Cardiac AL (n=227)         | 94 (42.7%)                           | <0.001  |
| Non-CAL (n=105)            | 19 (18%)                             |         |
| ≥0.1                       |                                      |         |
| Cardiac AL (n=227)         | 0.10 (0–16.5)                        | <0.001  |
| Non-CAL (n=105)            | 0.03 (0–0.07)                        |         |
| NT-proBNP, ng/L            |                                      |         |
| Cardiac AL (n=227)         | 4,566 (222–103,277)                 | <0.001  |
| Non-CAL (n=105)            | 151 (7–890)                          |         |
| ≥5,000                     |                                      |         |
| Cardiac AL (n=227)         | 103 (47.2%)                          | <0.001  |
| Non-CAL (n=105)            | 0                                    |         |
| ≥8,500                     |                                      |         |
| Cardiac AL (n=227)         | 66 (30.3%)                           | <0.001  |
| Non-CAL (n=105)            | 0                                    |         |
| BNP, ng/L                  |                                      |         |
| Cardiac AL (n=227)         | 691 (53–5,000)                       | <0.001  |
| Non-CAL (n=105)            | 42 (5–116)                           |         |
| Pleural effusion           |                                      |         |
| Cardiac AL (n=227)         | 87 (37.4%)                           | <0.001  |
| Non-CAL (n=105)            | 2 (1.9%)                             |         |
| Mayo stage                 |                                      |         |
| n=217                      | 108 (49.8%)                          | <0.001  |
| n=100                      | 10 (10%)                             |         |
| I                          | 2 (0.9%)                             | 90 (90%) |
| II                         | 108 (49.8%)                          | 10 (10%) |
| III                        | 107 (49.3%)                          | 0       |
| IIIb                       | 44 (20.3%)                           | 0       |
| Echocardiography           |                                      |         |
| n=217                      | 14.2±3.8                             | <0.001  |
| n=95                       | 9±1.5                                |         |
| IVS, mm                    |                                      |         |
| Cardiac AL (n=227)         | 12.8±2.8                             | <0.001  |
| Non-CAL (n=105)            | 8±1.3                                |         |
| LVFW, mm                   |                                      |         |
| Cardiac AL (n=227)         | 57 (21–88)                           | <0.001  |
| Non-CAL (n=105)            | 66.5 (52–84)                         |         |
| LVEF, %                    |                                      |         |
| Cardiac AL (n=227)         | 63 (29%)                             | <0.001  |
| Non-CAL (n=105)            | 0                                    |         |
| LVEF <48%                  |                                      |         |
| E/A*                       | 1.6±0.8                              | 0.07     |
| E/E*                       | 17 (8–42)                            | NA      |
| CMR                        |                                      |         |
| n=74                       | 69 (93.2%)                           | NA      |
| LGE                        | 63.7 (32.9–90.3)                     |         |
| LVEDV index                |                                      |         |
| Cardiac AL (n=227)         | 63 (21–107)                          | <0.001  |
| Non-CAL (n=105)            | 56 (30–80)                           |         |
| RVEDV index                |                                      |         |
| Cardiac AL (n=227)         | 52.5 (25.5–74.2)                     |         |
| Non-CAL (n=105)            | 58 (21–107)                          |         |
| Endomyocardial biopsy      |                                      |         |
| n=59                       | 58 (98.3%)                           | NA      |
| Congo red stain            |                                      |         |

AL, light-chain amyloidosis; CAL, AL with cardiac involvement; BNP, B-type natriuretic peptide; cTnI, cardiac troponin I; E/A, ratio of E and A; E/E’, ratio of E and E’; IVS, interventricular septal thickness; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVFW, left ventricular posterior wall thickness; CMR, cardiac magnetic resonance imagining; NA, not acquired; NT-proBNP, N-terminal fragment of B-type natriuretic peptide; NYHA, New York Heart Association; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; SBP, systolic blood pressure.

Results

Demographic, Clinical and Cardiac Characteristics
During the study period, 332 patients were newly diagnosed with AL; of them, 227 (68.4%) had cardiac AL and 105 did not. The demographic and clinical characteristics of both groups are compared in Table 1. CAL patients had a median age of 57.0 years, and the ratio of male to female was 2.0:1. Compared with non-CAL patients, CAL patients had a higher median serum dFLC concentration, and more patients had bone marrow plasma cells ≥10%. CAL patients had more gastrointestinal and peripheral neuropathic involvement but less renal involvement. More than one-third of CAL patients had ≥3 organs involved, which was more than in the non-CAL patients. When biomarkers were evaluated, CAL patients had a lower median level of 24-h urine protein, but a higher median level of serum albumin.

Cardiac parameters in CAL patients are listed in Table 2. About half of them were in NYHA Class III or IV and had SBP <100 mmHg. The median value of the different cardiac biomarkers was 4,566 ng/L (range, 222–103,277) for NT-proBNP and 0.10 ng/mL (range, 0–16.5) for cTnI; 103 patients (47.2%) and 66 patients (30.3%) had NT-proBNP ≥5,000 ng/L and 8,500 ng/L, respectively. Among all the
Congo red stain was positive in 98.3% of endomyocardial biopsy specimens, and the only patient with negative Congo red stain was proved to have CAL by laser microdissection with mass spectrometry-based proteomic analysis. Therefore, the sensitivity of endomyocardial biopsy was as high as 100%.

**Treatment and Response**

**First-Line Treatment**

A total of 50 patients (22.0%) received palliative treatment. Of the remaining 177 patients, 7 patients (3.1%) received ASCT, 100 (44.1%) received bortezomib combinations, and 70 (30.8%) received non-bortezomib regimens (melphalan-dexamethasone, n=43; thalidomide-dexamethasone/thalidomide-cyclophosphamide-dexamethasone, n=17; and lenalidomide combinations, n=10).

**Hematological Response**

Of the 177 patients who received first-line treatment, 40 were excluded for the following reasons: 16 stopped after 1 or 2 cycles of chemotherapy because of toxicity or economic problems; 24 did not attend the first follow-up visit within 3 months after diagnosis. Therefore, 137 patients were evaluated for response. The hematological responses are listed in Table 3. An overall hematological response was achieved in 6 ASCT patients (85.7%). The bortezomib group had a higher overall hematological response than the non-bortezomib group (66.2% vs. 46.8%, P=0.030). The median time from treatment to hematological response was 4, 1, and 4 months in the ASCT, bortezomib and non-bortezomib groups, respectively.

**Cardiac Response (CarR)**

In the 137 evaluable patients, organ response was achieved in 56 patients (40.9%) and CarR in 51 (37.2%) (Table 3). The median time from treatment to CarR was 5 months (1–21 months). CarR was more frequently associated with hematological complete response (36 of 49 patients, 73.5%) and VGPR (11 of 20 patients, 55%) than with PR (4 of 14 patients, 28.5%) (P=0.019). CarR was achieved in 44.6% of the 83 patients in the bortezomib group, which was statistically higher than the non-bortezomib group (23.4%, P=0.002).

All patients with CarR showed a decrease of ≥30% in NT-proBNP, which declined from a median value of 3,389 ng/L (range, 349–16,496) to 740 ng/L (range, 64–6,000), and a decreased rate of 71% (range, 32–97%) was noted. A total of 41 of these patients (80.4%) achieved an improvement of at least 1 grade in NYHA Class; 10 patients with a hematological response ≥VGPR underwent repeated cardiac MRI and of them, 5 (50%) had a reduction of ≥2 mm

### Table 3. Hematological and Cardiac Responses

| Hematological Response | ASCT (n=7) | Bortezomib group (n=83) | Non-bortezomib regimen (n=47) |
|------------------------|------------|-------------------------|-------------------------------|
| CR                     | 5 (71.4%)  | 30 (36.1%)              | 14 (29.8%)                    |
| VGPR                   | 1 (14.3%)  | 15 (18.1%)              | 4 (8.5%)                      |
| PR                     | 0          | 10 (12.0%)              | 4 (8.5%)                      |
| NR                     | 1 (14.3%)  | 28 (33.7%)              | 25 (53.2%)                    |
| ORR                    | 37.2%      | 66.2%                   | 46.8%                         |
| CarR                   | 42.9%      | 44.6%                   | 23.4%                         |

ASCT, autologous stem cell transplantation; CarR, cardiac response; CR, complete hematological response; HemR, hematological response; NR, no response; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

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CAL patients, 49.8% had Mayo stage II disease, 49.3% had stage III disease, and only 2 patients had stage I disease. Of the patients with stage III disease, the number with stage IIIa disease was about 1.5-fold the number with stage IIIb disease. Echocardiography was performed in 217 patients (95.6%). The mean LV wall thickness was 14.2±3.8 mm, and the median EF was 57% (range, 21–88%). Cardiac MRI was done in 74 patients (32.6%) and late gadolinium enhancement was positive in 69 patients (93.2%). Endomyocardial biopsy was performed in 59 patients (26.0%);
bortezomib treatment, or advanced cardiac amyloid had worse hematological responses with significant difference (Supplementary Table).

Survival
Median follow-up time was 28 months (2–123 months) for all patients. At the time of last follow-up, 15 patients (6.6%) had been lost and 116 (51.1%) had died. The median OS was 17 months [95% confidence interval (CI) 10.7–23.3], and the 3, 6, 12, and 24-month OS rates were 72.6%, 66.3%, 53.0%, and 44.6%, respectively (Figure 1A). The median OS for patients with Mayo stage II, IIIa or IIIb disease was 22, 19, and 3 months, respectively (P<0.001) (Figure 1B).

With regard to treatment options, all ASCT patients remained alive, and palliative patients had a median OS of only 3 months (95% CI 1.9–4.1). The median OS in patients treated with chemotherapy was 29 months (95% CI 17.5–40.5), which was longer than that in patients with palliative treatment (P<0.001). The median OS was not reached in patients treated with bortezomib combinations, compared with 18 months in the non-bortezomib group (P=0.205). In patients with Mayo stage III disease, the bortezomib group survived longer than the non-bortezomib group (median OS, 30 vs. 10 months, P=0.051) (Figure 2). In patients with

in septal thickness, 2 (20%) showed an improvement of ≥10% in LVEF and 5 (50%) showed an improvement of ≥10% in right ventricular EF. Of the 5 patients with a hematological response ≥VGPR underwent repeated echocardiography, 4 (80%) had a reduction of ≥2 mm in septal thickness and 2 (40%) showed an improvement of ≥10% in LVEF.

Male patients and those with kappa-type, gastrointestinal involvement, ≥3 involved organs, SBP <100 mmHg, non-
Mayo stage III disease who survived for >1 month, the bortezomib group survived significantly longer than the non-bortezomib group (median OS, not reached vs. 12 months, P=0.019).

Survival was significantly associated with hematological response (Figure 3A). Survival rates at 12 and 24 months for patients evaluable for a hematological response were: for patients with complete response, both 96%; for patients with VGPR or PR, 83.8% and 77.8%; for non-responders, 20.7% and 14.8% (P<0.001). The OS for hematological responders with CarR was longer than that for patients without CarR (P<0.001) (Figure 3B).

### Univariate and Multivariate Analyses of OS

Risk factors associated with OS on univariate and multivariate analyses are given in Table 4. Using ROC analysis, the NT-proBNP cutoff identified for death at 1 year was 5,000 pg/mL [area under the curve (AUC), 0.730; P<0.001], the SBP cutoff was 100 mmHg (AUC, 0.635; P=0.001) and the LVEF cutoff was 48% (AUC, 0.634; P=0.001). The OS for hematological responders with CarR was longer than that for patients without CarR (P<0.001) (Figure 3B).

### Discussion

In this retrospective cohort study, we analyzed 227 consecutive patients with CAL in a single center in China. Our study had 2 novel findings. First, we emphasized that bortezomib combinations given as first-line treatment were superior to non-bortezomib regimens, especially in patients with Mayo stage III disease. Second, using Cox regression analysis, we disclosed some baseline risk factors for the outcome that differed from those reported in the literature. Although not statistically significant, we showed that CAL patients had a longer duration from symptom onset to diagnosis. Furthermore, in the univariate analysis, we revealed that symptom-to-diagnosis interval >6 months was a risk factor associated with OS. Early detection allows for treatment that can halt cardiac damage, potentially reducing the risk for sudden death; therefore, timely examinations for early diagnosis and treatment are imperative. In patients highly suspected of CAL, if initial assessment of amyloid from less-invasive sites, such as the tongue, periumbilical fat, labial salivary gland, or bone marrow biopsy specimen is negative, cardiac biopsy should be considered, which has a sensitivity of 100% when obtaining a pathological diagnosis and conclusively identifies CAL. As well, Austin et al showed that late gadolinium enhancement by cardiac MRI had a high sensitivity of 88% and specificity of 95% in patients with biopsy-proven amyloidosis. Our study also showed that late gadolinium enhancement by cardiac MRI had a high sensitivity of 93.2%. Therefore, CMR evaluation is recommended as the first-line non-invasive diagnostic tool for CAL. In our cohort, endomyocardial biopsy was performed in 26.0%, and CMR was done in 32.6% of all patients, which were high percentages, enhancing the credibility of the present study.

Although the OS for CAL has improved in the past 3
decades, early death in CAL remains an obstacle to improving outcomes, and half of the patients with Mayo stage III disease die within 3 months, which was also demonstrated in our study. Bortezomib, the first therapeutic proteasome inhibitor, has limited cardiotoxicity, and was found in our study and reported in the literature to have a median time to first response of 1–2 months, which was shorter than in the ASCT and non-bortezomib groups. Both prospective and retrospective studies of AL patients treated with bortezomib showed high hematological response rates (68–71%), and the combination of bortezomib, dexamethasone and cyclophosphamide increases the hematological response rate to 94%. Concerning CAL, a combination of bortezomib, dexamethasone and an alkylating agent (BDex+AA) was proved to have a hematological response rate of 68–96%, and a CarR rate of 32–60%, which was higher than that in the non-bortezomib group. Furthermore, a study in 106 CAL patients with symptomatic heart failure showed that BDex+AA improved survival more than in the non-bortezomib group. In our cohort with more patients included, we also demonstrated that bortezomib combinations significantly improved hematological response and CarR compared with non-bortezomib regimens. We also showed that bortezomib combinations improved median OS significantly in CAL patients with Mayo stage III who survived for >1 month when the response of bortezomib could be observed. Therefore, bortezomib combinations are recommended for naïve patients with significant Mayo stage III CAL and those refractory to other therapies.

Wechalekar et al explored predictors of OS in 346 CAL patients with Mayo stage III disease and demonstrated that NT-proBNP ≥ 8,500 pg/mL and SBP < 100 mmHg were the only factors that independently affected OS. Risk factors described in other studies include NYHA functional class, estimated glomerular filtration rate, response to chemotherapy, amyloid load, age, elevation of cTnI, and LV systolic or diastolic dysfunction. We identified 3 independent risk factors for OS: NT-proBNP ≥ 5,000 pg/mL, bone marrow plasma cells ≥ 10%, and SBP < 100 mmHg were independent risk factors for OS.

Study Limitations

First, because of its retrospective nature, many patients were lost and may have been a source of bias. Second, our hospital has undertaken the FLC assay only since 2012, so serum FLC concentrations before 2012 were not available. Third, because of its complexity, we did not analyze the influence of second-line therapy on survival. Despite these limitations, we tried our best to obtain full information for 227 CAL patients, and provide some meaningful characteristics and outcomes.

In summary, using a series of CAL patients in whom a high proportion were diagnosed by cardiac biopsy and evaluated with CMR, we showed that CAL patients had a poor prognosis, especially those with Mayo stage III disease. Patients treated with bortezomib combinations had a better hematological response rate and CarR than the non-bortezomib group. Furthermore, bortezomib combinations improved median OS significantly in CAL patients with Mayo stage III who survived for >1 month.

NT-proBNP ≥ 5,000 pg/mL, bone marrow plasma cells ≥ 10%, and SBP < 100 mmHg were independent risk factors for OS.

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Disclosures

None.

References

1. Merlini G, Seldin DC, Gertz MA. Amyloidosis: Pathogenesis and new therapeutic options. J Clin Oncol 2011; 29: 1924–1933.
2. Kyle RA, Greipp PR, O’Fallon WM. Primary systemic amyloidosis: Multivariate analysis for prognostic factors in 168 cases. Blood 1986; 68: 220–224.
3. Falk RH, Comenzo RL, Skinner M. The systemic amyloidoses. N Engl J Med 1997; 337: 989–909.
4. Kyle RA, Gertz MA. Primary systemic amyloidosis: Clinical and laboratory features in 474 cases. Semin Hematol 1995; 32: 45–59.
5. Kumar SK, Gertz MA, Lacy MQ, Dingli D, Hayman SR, Buadi FK, et al. Recent improvements in survival in primary systemic amyloidosis and the importance of an early mortality risk score. Mayo Clin Proc 2011; 86: 12–18.
6. Muchtar E, Gertz MA, Kumar SK, Lacy MQ, Dingli D, Buadi FK, et al. Improved outcomes for newly diagnosed AL amyloidosis between 2000 and 2014: Crazing the glass ceiling of early death. Blood 2017; 129: 2111–2119.
7. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet 2016; 387: 2641–2654.
8. Wechalekar AD, Schonland SO, Kastritis E, Gillmore JD, Dimopoulos MA, Lane T, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood 2013; 121: 3420–3427.
9. Gertz MA, Comenzo R, Falk RH, Fermand JP, Hazenberg BP, Hawkins PN, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): A consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18–22 April 2004. Am J Hematol 2005; 79: 319–328.
10. Palladini G, Dispenzieri A, Gertz MA, Kumar S, Wechalekar A, Hawkins PN, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: Impact on survival outcomes. J Clin Oncol 2012; 30: 4541–4549.
11. Sun W, Sun J, Zou L, Shen K, Zhong D, Zhou D, et al. The successful diagnosis and typing of systemic amyloidosis using a multiwave-associate flow cytometry fast sample preparation method and LC/MS/MS analysis. PLoS One 2015; 10: e0127180.
12. Dispenzieri A, Gertz MA, Kyle RA, Lacy MQ, Burritt MF, Therneau TM, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: A staging system for primary systemic amyloidosis. J Clin Oncol 2004; 22: 3751–3757.
13. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol 2012; 30: 989–995.
14. Palladini G, Sachdeva S, Hanham S, Milan F, Gillmore J, Foti A, Lachmann H, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood 2015; 126: 612–615.
15. Li J, Feng J, Cao XX, Zhang CL, Shen KN, Huang XF, et al. Autologous peripheral blood hematopoietic stem cell transplantation for patients with primary light chain amyloidosis: Experience of 31 cases in a single center. Zhonghua Xue Ye Xue Za Zhi 2016; 37: 201–204 (in Chinese).
16. Grogan M, Dispenzieri A. Natural history and therapy of AL cardiac amyloidosis. Heart Fail Rev 2013; 18: 155–162.
17. Gertz MA, Grogan M, Kyle RA, Tajik AJ. Endomyocardial biopsy-proven light chain amyloidosis (AL) without echocardiographic features of infiltrative cardiomyopathy. Am J Cardiol 1997; 80: 93–95.
18. Austin BA, Tang WH, Rodriguez ER, Tan C, Flamm SD, Taylor DO, et al. Delayed hyper-enhancement magnetic resonance
imaging provides incremental diagnostic and prognostic utility in suspected cardiac amyloidosis. *JACC Cardiovasc Imaging* 2009; 2: 1369–1377.

19. Lin L, Li X, Feng J, Shen KN, Tian Z, Sun J, et al. The prognostic value of T1 mapping and late gadolinium enhancement cardiovascular magnetic resonance imaging in patients with light chain amyloidosis. *J Cardiovasc Magn Reson* 2018; 20: 2.

20. Reece DE, Hegenbart U, Sanchorawala V, Merlini G, Palladini G, Blade J, et al. Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: Results of a phase 1/2 study. *Blood* 2011; 118: 865–873.

21. Mikhail JR, Schuster SR, Jimenez-Zepeda VH, Bello N, Spong J, Reeder CB, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. *Blood* 2012; 119: 4391–4394.

22. Kastritis E, Wechalekar AD, Dimopoulos MA, Merlini G, Hawkins PN, Perfetti V, et al. Bortezomib with or without dexamethasone in primary systemic (light chain) amyloidosis. *J Clin Oncol* 2010; 28: 1031–1037.

23. Venner CP, Lane T, Foard D, Rannigan L, Gibbs SDJ, Pinney JH, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. *Blood* 2012; 119: 4387–4390.

24. Jaccard A, Comenzo RL, Hari P, Hawkins PN, Roussel M, Morel 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: 1479–1485.

25. Sayago I, Krsnik I, Gomez-Bueno M, Garcia-Pavia P, Jaramillo N, Salas C, et al. Analysis of diagnostic and therapeutic strategies in advanced cardiac light-chain amyloidosis. *J Heart Lung Transplant* 2016; 35: 995–1002.

26. Sperry BW, Ikram A, Hachamovitch R, Valent J, Vranian MN, Phelan D, et al. Efficacy of chemotherapy for light-chain amyloidosis in patients presenting with symptomatic heart failure. *J Am Coll Cardiol* 2016; 67: 2941–2948.

27. Mankad AK, Sesay I, Shah KB. Light-chain cardiac amyloidosis. *Curr Probl Cancer* 2017; 41: 144–156.

28. Kristen AV, Brokhals E, Aus dem Siepen F, Bauer R, Hein S, Aurich M, et al. Cardiac amyloid load: A prognostic and predictive biomarker in patients with light-chain amyloidosis. *J Am Coll Cardiol* 2016; 68: 13–24.

29. Lee MH, Lee SP, Kim YJ, Sohn DW. Incidence, diagnosis and prognosis of cardiac amyloidosis. *Korean Circ J* 2013; 43: 752–760.

30. Kourelis TV, Kumar SK, Gertz MA, Lacy MQ, Buadi FK, Hayman SR, et al. Coexistent multiple myeloma or increased bone marrow plasma cells define equally high-risk populations in patients with immunoglobulin light chain amyloidosis. *J Clin Oncol* 2013; 31: 4319–4324.

**Supplementary Files**

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