BRIEF COMMUNICATION

Efficacy of bortezomib, cyclophosphamide and dexamethasone in cardiac AL amyloidosis

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Abstract

Cardiac light chain (AL) amyloidosis is a condition with a very poor prognosis. We report a retrospective analysis comparing the traditional melphalan and dexamethasone protocol with cyclophosphamide, bortezomib and dexamethasone in late-stage cardiac AL amyloidosis. The primary end points were overall survival and haematological response. Both regimens provided meaningful responses in this difficult to treat patient group.

Amyloidosis refers to a group of diseases characterised by constitutive proteins that are deposited extracellularly. Light chain (AL) amyloidosis arises from deposition of monoclonal light chains produced by malignant plasma cells in the bone marrow. Organs most commonly affected are the kidneys, heart, nervous system and gastrointestinal tract. Multicentre data confirm the poor prognosis of cardiac amyloidosis; up to 49% of patients with AL amyloidosis died or experienced cardiac complications within 2 years of diagnosis.[1] Chemotherapy is the backbone of treatment for AL amyloidosis with an aim to suppress the underlying plasma cell dyscrasia and halt amyloid production. Prolonged disease-free survival has been reported in a highly select group of patients who underwent sequential orthotopic heart transplantation followed by autologous haemopoietic stem cell treatment.[2]

Melphalan and prednisone was a revolutionary treatment option first published in 1997 and the combination of melphalan and dexamethasone (MDex) followed, with higher response rates[3,4]; however, the high rates of responses were not reproducible in patients with severe cardiac involvement.[5] Bortezomib is a first-in-class

cytotoxic agent associated with potent and specific inhibition of proteasome that can lead to rapid haematological responses.[6] Kastritis et al. demonstrated a haematological response of 71%, including a complete remission rate of 25%, using a bortezomib-dexamethasone regimen in a pretreated population; however, 49% of patients died or had progression by a median of 12-month follow-up.[7] A recent phase III multicentre randomised trial compared MDex and bortezomib, melphalan and dexamethasone (BMDex). The BMDex group had significantly improved haematological response rates of 79% versus 52% ($P = 0.002$) and a 50% reduction in mortality rate.[8] These prospective data reinforced that all patients with AL amyloidosis require some bortezomib-based protocol as standard of care.[9] Outside of these trials, however, the commonest regimen used to treat patients with cardiac amyloidosis worldwide is bortezomib, cyclophosphamide and dexamethasone (CyBorD).[9] We report a retrospective analysis comparing the haematological responses and survival outcomes of patients with cardiac AL treated with subcutaneous CyBorD compared with MDex.

This was a single-centre retrospective study of consecutive patients treated for AL amyloidosis between 2005 and 2017 at St. Vincent's Hospital in Sydney, Australia. Forty-one patients with cardiac AL amyloidosis were

Conflict of interest: None.

Table 1 Baseline patient characteristics and haematological responses at 3 and 6 months

	MDex (*n* = 10)	CyBorD (*n* = 15)
Age (median, range), years	63 (49–84)	61(45–71)
Men, no. (%)	6 (60)	7 (46)
Mayo cardiac stage		
I	1	0
II	4	3
III	5	6
IV	0	6
Biological data		
Ejection fraction (%)	60 (40–65)	60 (40–68)
Troponin T (ng/L)	73 (19–203)	58 (13–483)
NT-proBNP (ng/L)	1818(415–7668)	3882 (938–10 385)
dFLC (mg/L)	344 (11–1587)	266 (31–2538)
fLC ratio	32 (2–123)	16 (2–228)
Plasma cell percentage on bone marrow aspirate	5.5 (1–17)	12.5 (7–31)
Haematological responses at 3 months		
Complete response	0	0
VGPR	2	4
PR	0	4
No response	4	3
dFLC not measured	2	1
Patients died at 3 months	2	2
Haematological responses at 6 months		
Complete response	0	0
VGPR	2	4
PR	1	5
No response	1	1
dFLC not measured	3	2
Patients died at 6 months	3	2

Abbreviations: CyBorD, bortezomib, cyclophosphamide and dexamethasone; dFLC, free light chain difference; fLC, free light chain; MDex, melphalan and dexamethasone; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PR, partial response; VGPR, very good partial response.
*One patient taking CyBorD was excluded from haematological responses because of cardiac transplantation.

identified from hospital databases; 16 were excluded for insufficient patient records. There were 15 in the CyBorD group and 10 in the MDex cohort. One patient from the CyBorD arm was excluded from the haematological response rates becuase of an early cardiac transplantation following AL amyloidosis diagnosis. Another patient in the CyBorD arm was excluded from the survival analysis for receiving a later transplantation following chemotherapy (total of 13 CyBorD patients in survival analysis). The primary objective was to compare overall survival between patients treated with MDex and CyBorD protocols. Haematological response was also compared between groups at 3 and 6 months from diagnosis using validated response criteria.[10] In particular, the free light chain difference (dFLC) was used to measure responses, with posttreatment dFLC <40 mg/L

classified as a very good partial response (VGPR) and a 50% drop in dFLC serum level was a partial response (PR).[10] Because of our small cohort, the criteria were simplified defining a 'haematological response' as a patient either having a VGPR or PR for the purposes of Figure 1. Patients with missing dFLC data at 3 and 6 months were also excluded from the haematological response rates. Other haematological baseline characteristics measured included free light chain (fLC) ratio and plasma cell percentage on bone marrow biopsy. Baseline cardiac variables including N-terminal pro-B-type natriuretic peptide (NT-proBNP), and troponin T were collected and used to measure the patient's Mayo cardiac stage along with dFLC, using 2012 revised criteria.[11] All baseline characteristics are expressed as median (range) (Table 1). The MDex protocol consisted of intravenous melphalan 16 mg/m^2 on day 1 and dexamethasone 20 to 40 mg/d orally on days 1 to 4 or weekly (at the investigators' discretion) of every 28-day cycle until two cycles beyond best response, to a maximum of six cycles.[12] The CyBorD regimen included subcutaneous bortezomib 1.3 mg/m^2, oral cyclophosphamide 300 mg/m^2 and oral dexamethasone 20 mg weekly for a minimum of 4 cycles.[9] The project was approved by the institutional ethics committee and conducted in accordance with National Health and Medical Research Council of Australia guidelines (HREC reference number: LNR/15/SVH/256). Survival was calculated using the Kaplan–Meier method using a log-rank test for group comparisons. Haematological response was assessed using Fisher exact test with significance defined (one-sided) as <0.05. Statistical analyses were performed using IBM SPSS statistics version 25.

A total of 15 patients received CyBorD (median age, 61 years; 46% men) and 10 patients received MDex chemotherapy (median age, 63 years; 60% men). A total of 80% of patients in the CyBorD group had Mayo cardiac stage III or IV disease compared with 50% of patients in the MDex group (*P* = 0.073) (see Table 1).

At baseline, the median left ventricular ejection fraction was 60% for both groups. The median NT-proBNP was 3882 ng/L (938–10 385 ng/L) in the CyBorD group and 1818 ng/L (415–7668 ng/L) in the MDex group. Median troponin T was 58 ng/L (13–483 ng/L) in the CyBorD group compared with 73 ng/L (19–203 ng/L) in the MDex group. In terms of baseline characteristics, the only significant difference was that the CyBorD group had higher plasma cell percentage rates on the initial bone marrow aspirate (12.5% [7–31]) versus the MDex group (5.5% [1–17]) (*P* = 0.041). dFLC was 266 mg/L (31–2538 mg/L) in the CyBorD group and 344 mg/L (11–1587 mg/L) in the MDex group. Serum fLC ratio at baseline was 16 (2–228) in the CyBorD and 32 (2–123)
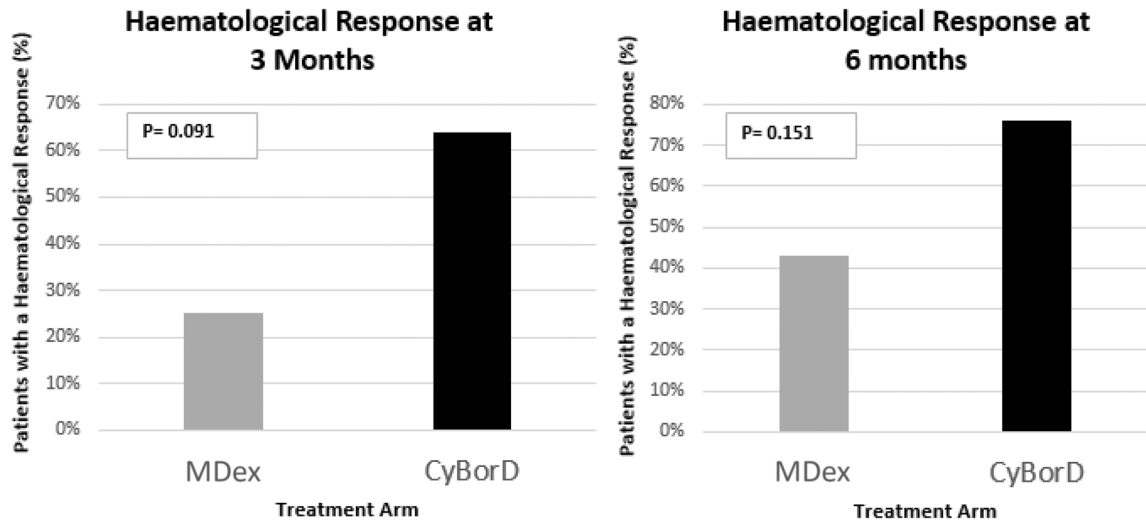
Figure 1 Haematological response (very good partial response or partial response) rates between patients with cardiac light chain amyloidosis in the melphalan and dexamethasone (MDex) and bortezomib, cyclophosphamide and dexamethasone (CyBorD) groups.
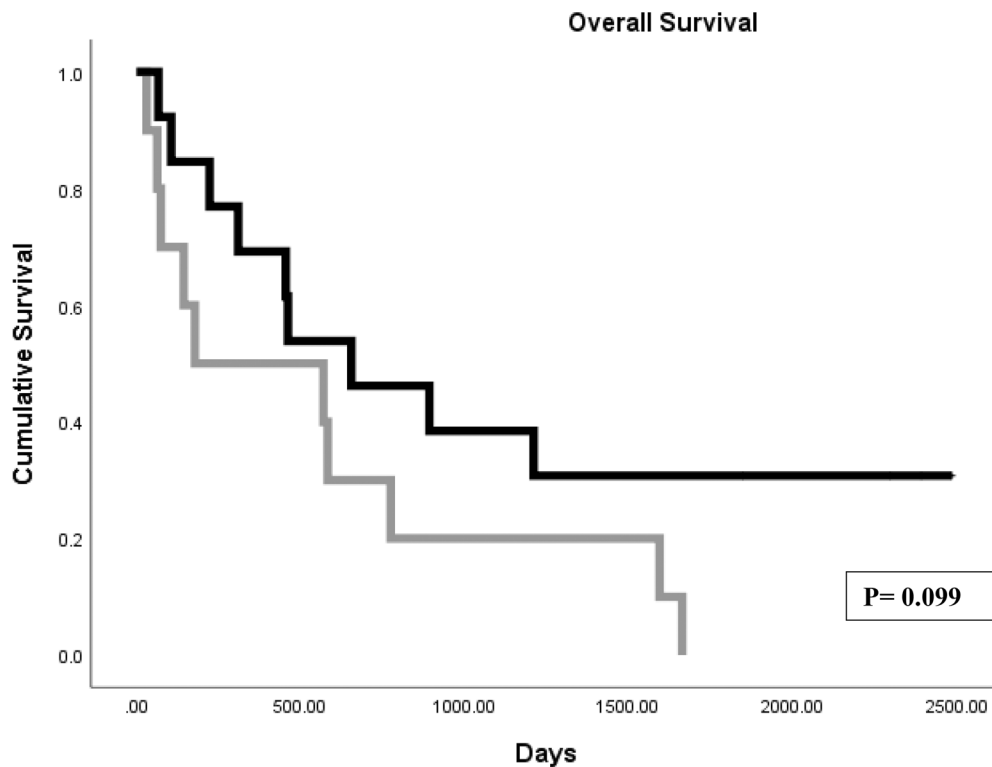
Figure 2 Survival curve for patients with cardiac light chain amyloidosis receiving bortezomib, cyclophosphamide and dexamethasone (CyBorD) versus melphalan and dexamethasone (MDex). (▭) MDex and (▬) CyBorD.

in the MDex group. The number of other organs affected was the same in both groups with a median of 1.

At 3 months after the treatment commenced, 62% of patients in the CyBorD group had a haematological response, and at 6 months this rose to 75% of patients (see Fig. 1). No patient in either group achieved a complete response. At the censor date for survival (1 June, 2021), four patients in the CyBorD group were still alive,

while no patients in the MDex group survived to this point. The median survival for the MDex group was 178 days (95% CI, 0–838 days) compared with the CyBorD group survival of 655 days (95% CI, 140–1169 days) ($P = 0.099$) (see Fig. 2). Two-year survival for the CyBorD group was 46% compared with 30% in the MDex group ($P = 0.319$).

Discussion

Cardiac AL amyloidosis is a condition with a poor prognosis. The current analysis demonstrates meaningful haematological responses in patients with cardiac AL amyloidosis treated with either MDex or CyBorD chemotherapy. There was a trend to increased overall survival in patients with cardiac AL amyloidosis who received CyBorD (see Fig. 2). This is despite the CyBorD cohort having a much higher rate of Mayo stage III/IV cardiac amyloidosis. While not statistically significant, the Kaplan–Meier curve separates early and trends towards long-term improved prognosis. The 1-year survival rate in the present study (69% in the CyBorD group) compares favourably with published 1-year survival rates in similar cohorts. A 2013 retrospective study of patients with stage III disease reported a 43% overall survival at 1 year; however, the vast majority of patients did not receive bortezomib-based regimens.[13] The same group has recently published a larger retrospective study of bortezomib-only treated patients confirming similar survival rates.[9] Jaccard et al. also showed a 1-year survival rate of 57% in 60 patients receiving CyBorD with stage III disease.

Underpinning the survival with chemotherapy were notable haematological responses in the CyBorD group (see Fig. 1). While not statistically significant, over three quarters of patients in the CyBorD group had either a VGPR or PR at 6 months. These haematological responses suggest possible superior efficacy over MDex and reaffirm the rapid onset of CyBorD response with a benefit seen as early as 3 months. Toxicity of bortezomib was not formally assessed but it is known to cause peripheral neuropathy, hypotension and worsening cardiac failure.[9] None of the patients in the CyBorD group in the current study ceased the regimen because of toxicity. Future treatment options for AL amyloidosis include daratumumab, a monoclonal antibody that binds to CD38 on plasma cells.[14] A recent large prospective multicentre randomised controlled trial demonstrated the benefit of daratumumab. When added to CyBorD, 53% of patients taking daratumumab achieved a complete haematological response compared with 18% in the CyBorD alone group.[15]

Limitations of the current study include a small sample size and potential population bias with 12 patients excluded because of missing data. The retrospective nature of the study meant some of the patients in the MDex group were treated over a decade earlier than those in the CyBorD group. There could be a period effect with regards to the improvements in supportive care over this time. Nevertheless, this analysis represents real-world data and demonstrates the difficulties of treating these complex patients who are often excluded from clinical trials.

In conclusion, this study demonstrated a trend to improved survival and superior haematological responses in patients with cardiac AL amyloidosis treated with CyBorD when compared with MDex. Despite these results, the treatment of patients with cardiac amyloidosis remains a significant unmet need in the field of amyloidosis management. Whether MDex, BMDex or CyBorD are the optimal regimens for advanced cardiac amyloidosis remains an unanswered question and will require trials specifically targeted at patients with Mayo stage IIIb disease.

Acknowledgements

References

1 Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. Circulation 2009; 120: 1203–12.

2 Davis P, Kale M, Liedtke S, Schrier S, Arai M, Wheeler R et al. Outcomes after heart transplantation for amyloid cardiomyopathy in the modern era. Am J Transplant 2015; 15: 650–8.

3 Kyle RA, Gertz MA, Greipp PR, Witzig TE, Lust JA, Lacy MQ et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. N Engl J Med 1997; 336: 1202–7.

4 Palladini G, Russo P, Nuvolone M, Lavatelli F, Perfetti V, Obici L et al. Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. Blood 2007; 110: 787–8.

5 Palladini G, Milani P, Foli A, Obici L, Lavatelli F, Nuvolone M et al. Oral melphalan and dexamethasone grants extended survival with minimal toxicity in AL amyloidosis: long-term results of a risk-adapted approach. Haematologica 2014; 99: 743–50.

6 Jaccard A, Comenzo RL, Hari P, Hawkins PN, Roussei M, Morel P et al. Efficacy of bortezomib,

cyclophosphamide and dexamethasone in treatment-naïve patients with high-risk cardiac AL amyloidosis (Mayo clinic stage III). *Haematologica* 2014; **99**: 1479–85.

7 Kastritis E, Wechalekar AD, Dimopoulos MA, Merlini G, Hawkins PN, Gillmore VP *et al*. Bortezomib with or without dexamethasone in primary systemic (light chain) amyloidosis. *J Clin Oncol* 2010; **28**: 1031–7.

8 Kastritis E, Leleu X, Arnulf B, Zamagni E, Cibeira MT, Kwok F *et al*. Bortezomib, melphalan, and dexamethasone for light-chain amyloidosis. *J Clin Oncol* 2020; **38**: 3252–60.

9 Manwani R, Cohen O, Sharpley F, Mahmood S, Sachchithanantham S, Foard D *et al*. A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib. *Blood* 2019; **134**: 2271–80.

10 Palladini G, Dispenzieri A, Gertz M, 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**: 4541–9.

11 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**: 989–95.

12 Mollee P, Campbell T, Cunningham I, Moore J, Prince HM, Cannell P *et al*. A phase II study of risk-adapted intravenous melphalan in patients with AL amyloidosis. *Br J Haematol* 2012; **157**: 766–8.

13 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**: 3420–7.

14 Sidiqi MH, Gertz MA. Daratumumab for the treatment of AL amyloidosis. *Leuk Lymphoma* 2019; **60**: 295–301.

15 Kastritis E, Palladini G, Minnema MC, Wechalekar AD, Jaccard A, Lee HC *et al*. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. *N Engl J Med* 2021; **385**: 46–58.