

# Treatment of Amyloid Light Chain Cardiac Amyloidosis: Systematic Review and Future Directions

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**Abstract: Background:** Several treatment strategies for amyloid light chain cardiac amyloidosis (AL-CA) have been described in the literature; however, there is no consensus about the optimal approach to AL-CA. **Objective:** We conducted this systematic review to summarize current evidence from published studies about the safety and efficacy of various treatment regimens for patients with AL-CA, mainly focusing on autologous stem cell transplant (ASCT) and heart transplant. **Methods:** An electronic literature search of PubMed, Web of Science, Scopus, EBSCO, and CINAHL Plus was conducted through December 2019 using the relevant keywords and prespecified MeSH terminology. Records were screened, and eligible studies were selected and narratively discussed. Data on the hematologic and cardiac responses as well as the safety of the treatment regimens were extracted and synthesized narratively in the context of the systematic review. **Results:** Thirty published articles were included in this systematic review. The most commonly used first-line treatment in the included studies was bortezomib-based therapy followed by high-dose

Keywords

Amyloidosis, cardiac, heart transplant

melphalan and ASCT, with recent evidence of improved outcome with the addition of daratumumab. Heart transplant was found to extend survival for selected patients who were not eligible for ASCT; however, it was found to affect the patients' tolerance of further chemotherapy in some studies. Published data on long-term outcomes with immunomodulatory agents were scarce. **Conclusion:** Current evidence suggests several possible regimens for the treatment of AL-CA. Effective treatment approaches for AL-CA include induction therapy with bortezomib-based or immunotherapy-based combinations in moderate/severe forms of cardiac involvement, followed by high-dose melphalan and ASCT in eligible patients, and heart transplant for selected severe cases. Therefore, we highlight the necessity of conducting well-designed, randomized controlled trials to provide evidence about the efficacy of these drugs with respect to ASCT.

## Background

Amyloid light chain amyloidosis (AL amyloidosis) is the second most common type of systemic amyloidosis after wild-type transthyretin amyloidosis, and is caused by overproduction of monoclonal free light chains by a plasma cell clone.<sup>1</sup> The deposition of the amyloidogenic light chains in organ tissues manifests as amyloid fibrils. The accumulation of AL fibrils in organs may lead to irreversible organ dysfunction and, ultimately, to rapid death if not properly treated. AL amyloidosis can affect virtually any solid organ (except the central nervous system); however, the most commonly affected organs are the heart, kidney, nerves, and liver.<sup>2</sup>

In AL amyloidosis, cardiac involvement is the main determinant of disease prognosis. Patients with AL cardiac amyloidosis (AL-CA) usually suffer from preserved or mildly reduced ejection fraction, increased myocardial wall thickness, severe diastolic dysfunction, and increased left ventricular filling pressure, which ultimately lead to severe heart failure and even death if not promptly treated at the early stage of the disease. Therefore, prompt diagnosis, appropriate staging, and treatment for AL amyloidosis are critical.

The main therapeutic goal of AL amyloidosis treatment is to decrease amyloid fibril formation and deposition by eliminating the pathological plasma cell clones that produce AL amyloid.<sup>3</sup> Planning the appropriate treatment strategy for patients with AL amyloidosis is challenging, and should be customized according to patient condition, stage of the disease, and the extent

of organ involvement.<sup>4,5</sup> Current treatment options for AL amyloidosis include chemotherapy and—for eligible patients—autologous stem cell transplant (ASCT). Individual therapies for isolated organ involvement may differ. For example, for isolated cardiac amyloidosis with severe heart failure, heart transplant may be the initial therapy of choice in highly selected cases. Most centers, however, require evidence of a deep hematologic response with a few cycles of initial therapy before proceeding with heart transplant.

Melphalan and dexamethasone was the standard first-line treatment for AL amyloidosis in earlier years, as supported by a single-arm study<sup>6</sup> and a randomized trial.<sup>7</sup> More recently, bortezomib-based and daratumumab (Darzalex, Janssen Biotech)-based regimens have come to be considered better choices as the standard of care for patients with AL amyloidosis.<sup>8,9</sup> Reports have shown that ASCT was associated with increased mortality in patients with elevated cardiac biomarkers and severe cardiac involvement.<sup>10</sup> Heart transplant has been reported to increase the survival of selected AL-CA patients with early and rapid response to initial chemotherapy.<sup>11,12</sup> Moreover, the sequence of chemotherapy before or after a heart transplant is not uniform, as demonstrated by Mignot and colleagues<sup>13</sup> in a series in which chemotherapy or ASCT were used before the transplant in some patients and after the transplant in other patients. Grogan and colleagues<sup>14</sup> reported data on 23 AL-CA patients who underwent heart transplant, in whom the median overall survival (OS) was 3.5 years. For those patients who achieved a hematologic complete response to either chemotherapy or ASCT, however, the median OS was significantly longer, at 10.8 years. Therefore, both careful patient selection and center experience with the existing therapeutic regimens are essential to improve the outcomes of patients with AL amyloidosis and cardiac involvement. Currently, no standard international guidelines exist for the treatment of AL-CA. Several treatment approaches have been reported in the literature. We conducted this systematic review to summarize current evidence from published studies about the safety and efficacy of various treatment strategies for patients with AL-CA.

## METHODS

We followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement during the preparation of this systematic review.<sup>15</sup>

### *Eligibility Criteria*

Studies satisfying the following eligibility criteria were included in the systematic review:

- (1) Population: studies of patients with AL amyloidosis and cardiac involvement
- (2) Intervention: studies in which the interventional group received any intervention to treat AL amyloid cardiomyopathy
- (3) Comparator: studies with no control group (single-arm studies) or studies with a control group receiving conventional management
- (4) Outcome: studies reporting at least one of the following outcomes: (1) cardiac response rate and (2) survival or mortality rate
- (5) Study design: studies that were described as randomized controlled trials (RCTs), quasi-experimental studies, single-arm clinical trials, and observational studies, whether prospective or retrospective

We excluded records in the following conditions:

- (1) Non-English articles whose data were insufficient in the English abstract
- (2) Theses
- (3) Conference abstracts
- (4) Articles whose data were not reliable for extraction and analysis

### **Literature Search**

A comprehensive literature search of PubMed, Web of Science, Scopus, EBSCO, and CINAHL Plus was conducted from the inception of the databases through December 2019. We used the following search query: [(AL amyloidosis (cardiovascular OR cardiomyopathy OR cardiac OR heart) (treatment [title] OR therapy [title]) AND transplant)].

### **Screening of Records**

Retrieved records from the literature search were screened in 2 steps. In the first step, the title and abstracts of all articles were screened for eligibility. In the second step, the full-text articles of eligible abstracts were retrieved and screened for eligibility.

### **Data Extraction**

Data were extracted from the studies and compiled on a uniform data extraction sheet. The extracted data included (1) characteristics of the included studies, (2) characteristics of the population of included studies, and (3) outcome measures.

## **RESULTS**

### **Study Selection**

The literature search yielded 340 records. After screening of titles and abstracts, 100 full texts were assessed for eligibility, leading to inclusion of 30 articles in this systematic review. Of the 30 articles, 17 described patients with AL

amyloidosis with cardiac involvement and 13 described patients with systemic AL amyloidosis, including a subgroup of patients with cardiac involvement. There was no uniformity in the definition of cardiac involvement with amyloidosis. We included only the data of patients with AL amyloidosis with cardiac involvement in the final sample of studies.

### **Study Characteristics**

The characteristics of the included studies are shown in Tables 1, 2, and 3. Included studies were heterogeneous in terms of the treatment regimens used, the study population, and the evaluation parameters. The most commonly used parameters were hematologic response, cardiac response, OS, and mortality.

### **Reported Treatment Regimens For AL-CA**

The treatment regimens reported in the included studies consisted of combinations of the following treatment lines: ASCT; bortezomib and dexamethasone (BD); daratumumab, bortezomib, cyclophosphamide, and dexamethasone (dara-CyBorD); high-dose melphalan therapy (HDM); melphalan and dexamethasone; oral melphalan, thalidomide, and reduced-intensity dexamethasone (MTD); heart transplant; and the SynCardia Total Artificial Heart from SynCardia Systems. The most commonly used first-line treatment in the included studies was bortezomib combination therapy followed by HDM/ASCT. For patients with severe CA and those who are not eligible for ASCT, the most common regimen was melphalan and dexamethasone followed by heart transplant.

### **HDM/ASCT**

In a study published in 2015, Kongtim and colleagues analyzed data on 30 patients treated with HDM/ASCT.<sup>16</sup> The 3-year OS with HDM/ASCT was 83%, and the 3-year cumulative incidence of relapse was 38.5%. In an RCT published in 2004, Sancharawala and colleagues compared HDM/ASCT as initial treatment vs 2 cycles of oral melphalan and prednisone followed by HDM/ASCT in previously untreated patients with AL systemic amyloidosis (of whom 46% had cardiac involvement).<sup>17</sup> They found that some patients with AL amyloidosis with cardiac involvement appeared to experience a survival disadvantage if HDM/SCT was delayed by initial treatment with standard oral chemotherapy. In another RCT by Huang and colleagues,<sup>18</sup> the HDM/ASCT regimen achieved a cardiac response in 25% of patients after 12 months and 50% of patients after 24 months. However, these response rates were augmented in the experimental group by the inclusion of a bortezomib-based regimen before the HDM/ASCT therapy, as discussed in the following section.

**Table 1.** Characteristics of the Studies in Patients With AL-CA

Study	Design	Intervention	N	Median Age, y	Sex (% M)	Outcome
Feng (2019) <sup>16</sup>	Prospective study	<ul style="list-style-type: none"> <li>• 3.1% ASCT</li> <li>• 44.1% BD</li> <li>• 30.8% non-Bor regimen</li> <li>• 22.0% palliative treatment</li> </ul>	227	57	66.5%	Cardiac responses: <ul style="list-style-type: none"> <li>• All evaluable patients: 37.2%</li> <li>• ASCT: 3 (42.9%)</li> <li>• Bor: 37 (44.6%)</li> <li>• Non-Bor regimen: 11 (23.4%)</li> </ul>
Qualls (2019) <sup>18</sup>	Case series	HT, then IMiD	3	51.3	66.6%	<ul style="list-style-type: none"> <li>• Acute rejection (n=2)</li> <li>• Well tolerated (n=1)</li> </ul>
Arnall (2019) <sup>19</sup>	Case report	5 cycles of CyBorD, then DaraPom-Dex	1	43	1 F	Failure of CyBorD after 5 cycles owing to symptoms worsening. Switching to DaraPom-Dex was more effective for this case of severe AL amyloidosis with cardiac involvement.
Adam (2018) <sup>20</sup>	Case series	Patient 1: twice HDM/ASCT; patient 2: HDM/ASCT, then HDM/BD; patient 3: HT, then immunosuppressive therapy containing prednisone; patient 4: HDM; patient 5: Bor-based therapy	5	60	80%	Complete remission of AL amyloidosis was achieved in all the patients. HT was the first step, which made the patients with severe HF (not tolerating any efficient therapy of AL amyloidosis) capable of undergoing intense treatment for AL amyloidosis.
Hamon (2016) <sup>21</sup>	Prospective study	ICD	45	66	77.7%	Appropriate ICD therapies are common (27%) in CA patients. No specific strong predictor of VA could be identified. However, patients with advanced heart disease, especially with AL-CA, display a poorer outcome.
Grogan (2016) <sup>14</sup>	Retro-spective analysis	HT, then chemo or ASCT	23	53	48%	Survival rates were 77%, 65%, and 43% at 1, 2, and 5 y after transplant. Rejection occurred in 8/23 patients after a median duration of 1.8 mo following transplant. However, for those who achieved a hematologic CR to chemo or ASCT, survival extended to 10.8 y.
Kongtim (2015) <sup>22</sup>	Retro-spective analysis	HDM/ASCT	30	53	73%	3-y OS from HDM/ASCT was 83%. Cumulative incidence of relapse at 3 y was 38.5%. Negative factors affecting survival included age >60 y, lack of novel induction therapy, and BM plasmacytosis >10%.
Spiliopoulos (2014) <sup>23</sup>	Case report	Artificial heart	1	74	1 M	After 1 y, the patient could practice daily life activities and quality of life improved (NYHA class I-II).
Gilstrap (2013) <sup>24</sup>	Retro-spective analysis	HT	31	56	72%	In AL-CA patients, survival after HT was similar to survival after HT for other cardiomyopathies. Low BMI was a predictor of survival.
Meyers (2013) <sup>11</sup>	Case report	HT	1	68	1 F	Patient had an excellent hematologic response to BD. Follow-up therapy with Len was started, and the patient quickly had a fatal allograft rejection of the heart and kidney. The findings support the theory that Len may have stimulated the immune system and precipitated the fatal rejection episode.

**Table 1.** (Continued) Characteristics of the Studies in Patients With AL-CA

Study	Design	Intervention	N	Median Age, y	Sex (% M)	Outcome
Adam (2013) <sup>12</sup>	Case series	HT	3	55	66.6%	An examination of the woman in this series 3 mo after HT showed that the original pathological values of free light chains became normal. The woman had ~8% of clonal plasma cells before HT. 3 mo after HT, BM contained only 3% of polyclonal plasma cells. In this case, the immunosuppressive treatment with corticosteroids after HT probably induced a hematologic CR. The woman was in CR from AL amyloidosis 7 mo after HT.
Palladini (2009) <sup>17</sup>	Retro-spective analysis	MTD	22	64	64%	6 patients died owing to CA before completing cycle 3. Early death was associated with reduced EF. 8 patients achieved a hematologic response, and 4 achieved durable improvement of cardiac dysfunction.
Kristen (2009) <sup>28</sup>	Retro-spective analysis	HT	19	53	50%	7 of 19 patients died while waiting for HT. The remaining 12 patients (CR, n=4) underwent surgery. Chemo in patients not in CR consisted of HDM/ASCT (n=5/12; subsequent CR, n=2; PR, n=3) or melphalan-prednisolone (PR, n=1). The 1- and 3-y survival rates were 83% and 83%, respectively.
Sack (2008) <sup>25</sup>	Prospective study	HT, then chemo	7	41.8	NA	All patients were alive after 4 y except 1 patient who died owing to infection 201 days after HT. As a first-line treatment for severe AL-CA, HT followed by chemo extends patient survival with promising results.
Mignot (2008) <sup>13</sup>	Retro-spective analysis	MD (n=5) or HDM/ASCT (n=1), then HT	8	48.5 (mean)	62.5%	After a median follow-up of 26 mo from HT, 6/8 patients were alive, and 4 had sustained hematologic remission.
Mignot (2008) <sup>26</sup>	Case report	MD, then HT	1a	45	1 M	After MD, which resulted in an 80% reduction of serum-free lambda light chain, the patient underwent orthotopic HT. 2 y later, he remained in sustained hematologic remission, with no evidence of allograft or extracardiac amyloid accumulation. MD may be considered as an alternative therapy in AL amyloid HT recipients ineligible for HDM/ASCT.
Dubrey (2004) <sup>27</sup>	Retro-spective analysis	HT	17	56	11/17	Survival was 50%, 50%, and 20% at 1, 2, and 5 y in those who underwent HT without chemo, and 71%, 71%, and 36% at 1, 2, and 5 y in those who also had chemo.

<sup>a</sup>This patient had heart failure related to restrictive cardiomyopathy, nephrotic syndrome, peripheral neuropathy, postural hypotension, macroglossia, and lambda light chain monoclonal gammopathy.

AL-CA, light chain cardiac amyloidosis; ASCT, autologous stem cell transplant; BD, bortezomib and dexamethasone; BM, bone marrow; BMI, body mass index; Bor, bortezomib; CA, cardiac amyloidosis; chemo, chemotherapy; CR, complete response/remission; DaraPom-Dex, daratumumab, pomalidomide, and dexamethasone; EF, ejection fraction; F, female; HDM, high-dose melphalan; HF, heart failure; HT, heart transplant; ICD, implantable cardioverter-defibrillator; IMiD, immunomodulatory drug; Len, lenalidomide; M, male; MD, melphalan and dexamethasone; mo, month(s); MTD, oral melphalan, thalidomide, and reduced-intensity dexamethasone; NA, not available; NYHA, New York Heart Association; OS, overall survival; PR, partial response/remission; VA, ventricular arrhythmia; y, year(s).

### ***Bortezomib-Based Combination Therapy***

Bortezomib-based combination therapies were used as a first-line treatment for induction before HDM/ASCT or ASCT alone. The inclusion of bortezomib in the treatment regimens was associated with increased cardiac responses. In a study by Feng and colleagues,<sup>19</sup> cardiac responses of 44.6% and 23.4% were achieved in patients with bortezomib-based treatments and non-bortezomib-based treatments, respectively. In the RCT by Huang and colleagues,<sup>18</sup> the addition of BD induction therapy before HDM/ASCT increased the cardiac response after 12 months (67% vs 25%) and 24 months (70% vs 50%) compared with the control group (HDM/ASCT without prior BD). In a third study, published by Jain and colleagues in 2018,<sup>20</sup> patients who received ASCT with prior bortezomib-based therapy had significantly higher cardiac responses compared with those who did not receive bortezomib-based therapy (75% vs 17%). Gupta and colleagues conducted a clinical trial to test the efficacy of induction with a bortezomib-based combination followed by HDM and ASCT on 27 patients with systemic amyloidosis, including some with cardiac involvement.<sup>21</sup> Cardiac responses were reported in 46% (6/13) after 6 months, 75% (9/12) after 1 year, 92% (11/12) after 2 years, and 88% at 5 years.

The BD regimen failed to achieve any cardiac response in the 15 patients with AL-CA in a clinical trial by Kastritis and colleagues.<sup>22</sup> Nonetheless, 3 out of the 15 patients had significant improvement in their heart failure status (New York Heart Association [NYHA] class improvement) with no need for diuretics. In a retrospective analysis, the BD regimen achieved a 3-year OS of 60%, but no information was reported on OS in the subgroup of AL-CA patients.<sup>23</sup>

### ***MTD Regimen***

The MTD regimen was described in a study in which Palladini and colleagues retrospectively analyzed data from 22 patients with severe AL-CA.<sup>24</sup> Of these patients, 6 with reduced ejection fraction died before completing cycle 3 of the treatment. Twelve patients achieved a significant improvement in terms of hematologic response or cardiac function. Therefore, the MTD regimen was tolerable and effective in patients with preserved ejection fraction, but not for those with reduced ejection fraction.

### ***The Daratumumab, Pomalidomide, and Dexamethasone Regimen***

The combination of cyclophosphamide, bortezomib, and dexamethasone was used in a 43-year-old woman with AL-CA who had symptomatic progression after 5 cycles. The patient was switched to the daratumumab, pomalidomide, and dexamethasone regimen, which was tolerated and effective after 2 cycles.<sup>25</sup>

### ***Dara-CyBorD Regimen***

The randomized phase 3 ANDROMEDA trial was designed to assess safety and efficacy of the addition of subcutaneous daratumumab to CyBorD in patients with AL amyloidosis.<sup>26,27</sup> A total of 388 patients were randomly assigned to receive dara-CyBorD (n=195) or CyBorD alone (n=193). Patients with advanced cardiac disease were excluded. A total of 71% of patients had cardiac involvement (23%, 40%, and 37% in cardiac stages I, II, and III, respectively).<sup>28</sup> The rate of overall cardiac response at 6 months was significantly higher with the dara-CyBorD regimen than with the CyBorD-alone regimen (42% vs 22% in stage I, 50.9% vs 29.6% in stage II, and 33.3% vs 15.9% in stage III).<sup>27,28</sup>

Based on the results of ANDROMEDA, the US Food and Drug Administration (FDA) granted accelerated approval to subcutaneous daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone for the treatment of newly diagnosed light chain amyloidosis. There was a concern about cardiac toxicity, so the approval of daratumumab/hyaluronidase (Darzalex Faspro, Janssen Biotech) by the FDA does not include patients with NYHA class IIIB or IV cardiac disease or Mayo 2004 stage IIIB (N-terminal pro-brain natriuretic peptide [NT-proBNP] >8500 ng/mL) disease.

Several clinical trials are evaluating the role of daratumumab in patients with advanced cardiac AL, including a trial of daratumumab monotherapy in patients with stage IIIB AL (NCT04131309), a trial of combination daratumumab/bortezomib and dexamethasone in patients with Mayo stage IV disease (NCT04474938), and a study of daratumumab, ixazomib, and dexamethasone in newly diagnosed AL amyloidosis patients (NCT03283917).

### ***Heart Transplant***

Qualls and colleagues described a series of 3 patients who underwent orthotopic heart transplant followed by immunomodulatory therapy.<sup>29</sup> Two of these patients had acute graft rejection and 1 patient tolerated the treatment and achieved a response. Organ rejection following immunomodulatory drug therapy has also been reported in renal and liver transplant in AL patients. Adam and colleagues reported a series of 3 patients with AL-CA who underwent heart transplant; all patients had a hematologic complete response after the procedure.<sup>12</sup> Sack and colleagues described a prospective study of heart transplant followed by chemotherapy in 7 patients with AL-CA and heart failure of NYHA class III or IV.<sup>30</sup> All patients were alive after 4 years, except 1 patient who died of infection 201 days after the transplant. Several reports showed the role of heart transplant in improving the survival of patients with severe AL-CA.<sup>13,14,31-36</sup> In some cases, patients received chemotherapy prior to the heart transplant, whereas in other

**Table 2.** Characteristics of the Studies on Systemic Amyloid Light Chain Amyloidosis Reporting Outcomes in the Subgroup of Patients With AL-CA

Study	Design	Intervention	Population (Subgroup With CA)	Median Age, y	Sex (% M)	Outcome
Palladini (2020) <sup>26-28</sup>	Prospective study	50% dara-CyborD; 50% CyborD	388 (275)	64	57%	Cardiac responses at 6 mo were significantly higher with dara-CyBorD (42% vs 22% in stage I).
Gupta (2019) <sup>21</sup>	Clinical trial	BD/HDM/ASCT	27 (13)	56	37%	After 5 y, hematologic CR was 100% and cardiac response was 88%. The median time to cardiac response was 6 mo.
Zhao (2016) <sup>23</sup>	Retro-spective analysis	(1) HT, (2) BD, (3) MD, or (4) prednisone-based regimens or no treatment	123 (68)	54 (mean)	67.4%	3-y OS rates of (1) 72%, (2) 60%, (3) 55%, and (4) 41%
Davis (2015) <sup>33</sup>	Retro-spective analysis	Chemo (n=8) followed by HT (n=9), then ASCT (n=5)	19 (9)	56 (mean)	44%	100% 1-y survival in patients with AL-CA
Sattian-ayagam (2010) <sup>35</sup>	Retro-spective analysis	HT with or without ASCT	45 (14)	56	56%	1-y and 5-y patient survival was 86% and 45% among HT recipients. Median patient survival was 9.7 y among 8/14 HT recipients who underwent subsequent ASCT and 3.4 y in 6 patients who did not undergo ASCT (P=.01).
Roig (2009) <sup>36</sup>	Retro-spective analysis	HT	25 (13)	54	54%	Of the 13 AL-CA patients, 9 died during follow-up (average, 4.5 y). Survival was poor in AL-CA patients undergoing HT.
Maurer (2007) <sup>34</sup>	Retro-spective analysis	HT with or without ASCT	25 (22)	55.5 (mean)	65%	AL-CA patients who received HT had a higher 1-y survival rate vs those who did not receive HT (80% vs 17%; P=.0005).
Kastritis (2007) <sup>22</sup>	Clinical trial	BD	18 (15)	60.5	44%	Overall, in all AL patients, 94% had a hematologic response. None of the AL-CA patients achieved cardiac responses as per the echocardiographic criteria, whereas 3 of the 15 patients had significant improvement in their heart failure status (NYHA classification improvement) with no need for diuretics or increased wall thickness.
Comenzo (1998) <sup>43</sup>	Clinical trial	Intensive melphalan + blood stem cell support	25 (8)	48	52%	After ~1-3 y post-treatment, 6 of the 8 patients with AL-CA achieved a cardiac response to intensive melphalan with blood stem cell support.

AL-CA, light chain cardiac amyloidosis; ASCT, autologous stem cell transplant; BD, bortezomib and dexamethasone; Bor, bortezomib; CA, cardiac amyloidosis; chemo, chemotherapy; CR, complete response/remission; dara-CyBorD, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; DaraPom-Dex, daratumumab, pomalidomide, and dexamethasone; F, female; HDM, high-dose melphalan; HT, heart transplant; M, male; MD, melphalan and dexamethasone; mo, month(s); MTD, oral melphalan, thalidomide, and reduced-intensity dexamethasone; NA, not available; NYHA, New York Heart Association; OS, overall survival; y, year(s).

**Table 3.** Characteristics of the Comparative Studies on Systemic AL Amyloidosis Reporting Outcomes in the Subgroup of Patients With AL-CA

Study	Design	Population (Subgroup With CA)	Intervention	Median Age, y	Sex (% M)	Outcome
Jain (2018) <sup>20</sup>	Retro-spective analysis	68 (26)	Bor-based therapy + ASCT	59.5	62%	Cardiac responses in the 2 groups were 12/16 (75%) vs 1/6 (17%), with a statistically significant difference ( $P=.01$ ).
			Non-Bor + ASCT	63	41%	
Huang (2014) <sup>18</sup>	RCT	56 (27)	BD/HDM/ASCT	53	64%	Cardiac responses after 12 mo • BD/HDM/ASCT: 67% (10/15) • HDM/ASCT: 25% (4/12)
			HDM/ASCT	51.5	57%	Cardiac responses after 24 mo • BD/HDM/ASCT: 70% (7/10) • HDM/SCT: 50% (3/6)
Jaccard (2007) <sup>7</sup>	RCT	100 (4)	HDM/ASCT	56.8	54%	Cardiac responses occurred in 4/24 and 3/23 in the HDM/ASCT and HDM/Dex groups, respectively.
			HDM/Dex	59.1	60%	
San-chorawala (2004) <sup>17</sup>	RCT	100 (22)	HDM/ASCT	57	52%	AL amyloidosis patients with cardiac involvement appeared to suffer a survival disadvantage if HDM/ASCT was delayed by initial treatment with standard oral chemo.
			2 cycles of oral MD, then HDM/ASCT	55	60%	

AL-CA, light chain cardiac amyloidosis; ASCT, autologous stem cell transplant; BD, bortezomib and dexamethasone; Bor, bortezomib; chemo, chemotherapy; dara-CyBorD, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; DaraPom-Dex, daratumumab, pomalidomide, and dexamethasone; Dex, dexamethasone; F, female; HDM, high-dose melphalan; HT, heart transplant; M, male; mo, month(s); MD, melphalan and dexamethasone; MTD, oral melphalan, thalidomide, and reduced-intensity dexamethasone; NA, not available; OS, overall survival; RCT, randomized controlled trial; y, year(s).

cases, ASCT followed the heart transplant in those who did not achieve a hematologic response.

**Melphalan and Dexamethasone Followed by Heart Transplant**

Mignot and colleagues described a case of a 45-year-old man with AL-CA with heart failure related to restrictive cardiomyopathy, nephrotic syndrome, peripheral neuropathy, postural hypotension, macroglossia, and lambda light chain monoclonal gammopathy.<sup>37</sup> After melphalan and dexamethasone therapy resulted in an 80% reduction of serum-free lambda light chain levels, he underwent orthotopic cardiac transplant. Two years later, he remained in sustained hematologic remission, with no evidence of allograft or extracardiac amyloid accumulation.

**SynCardia Total Artificial Heart**

Spiliopoulos and colleagues reported the case of a 74-year-old man with end-stage heart failure due to AL amyloidosis.<sup>38</sup> The patient was not eligible for heart transplant, so the SynCardia Total Artificial Heart was used as rescue therapy after failure of a left ventricular assist device. After 1 year, the patient’s quality of life improved and he could resume daily life activities (NYHA class I-II).

**DISCUSSION**

**Therapeutic Target and Treatment Lines for AL-CA**

Treatment in AL amyloidosis aims to normalize light chain levels and thereby alleviate disease symptoms and restore organ functionality. Several therapeutic agents can be used to reduce light chain levels. Most publications report on the use of the alkylating agent melphalan or the proteasome inhibitor bortezomib as first-line treatment. Other lines of treatment include immunomodulatory drugs, such as thalidomide (following low-dose melphalan), lenalidomide, and pomalidomide; proteasome inhibitors such as bortezomib (reversible), carfilzomib (Kyprolis, Amgen; irreversible), and ixazomib (Ninlaro, Millennium/Takeda Oncology; reversible); and monoclonal antibodies, such as daratumumab and isatuximab (Sarclisa, Sanofi Genzyme). Our systematic literature review identified a few controlled studies. However, these studies used different treatments and a variety of endpoints. Therefore, these data could not be analyzed quantitatively in a meta-analysis model.

The choice of the therapy in these studies was dependent on many factors, including the Mayo clinic staging related to the severity of cardiac involvement and level of



serum free light chain, the stage of heart failure according to NYHA class, and the degree of left ventricular dysfunction.

For previously untreated patients with moderate disease severity, bortezomib-based induction therapies were found to be promising as a first-line treatment. This treatment was commonly followed by HDM/ASCT. Recent data showed safety and efficacy with the addition of daratumumab to the CyBorD regimen, particularly an improvement in cardiac response rates when compared with CyBorD alone. This combination is considered a new standard-of-care induction regimen for AL amyloidosis patients by many international guidelines.

For patients who are not eligible for ASCT, a heart transplant as an initial treatment might be a reasonable choice in rare, selected cases. However, the decision to perform a heart transplant does not replace the need for chemotherapy to suppress the disease process. A heart transplant should not be performed when myocardial dysfunction is thought to be too advanced and irreversible, which would compromise the outcome of an orthotopic procedure. Orthotopic heart transplant should be reserved for patients with severe AL-CA and end-stage heart failure, given that Adam and colleagues reported that orthotopic heart transplant might compromise patients' ability to tolerate effective chemotherapy for AL amyloidosis.<sup>39</sup> Following orthotopic heart transplant, the choice of appropriate immunosuppressive therapies is an important consideration; the case reported by Meyers and colleagues supports the theory that lenalidomide might stimulate the immune system and lead to fatal rejection episodes after orthotopic heart transplant.<sup>11</sup> Data about the safety and efficacy of the other immunomodulators is scarce, and it is beyond the current literature to recommend their use in clinical practice owing to the lack of well-designed studies.

#### ***Studies Excluded From This Systematic Review***

We excluded studies of systemic AL amyloidosis that lacked data specifying the outcome of patients with cardiac involvement because these reports were beyond the research question of this systematic review. The studies by Sissoko and colleagues,<sup>40</sup> Gertz and colleagues,<sup>41</sup> and Seldin and colleagues<sup>42</sup> had an excellent methodology and included patients with cardiac involvement. However, data about the cardiac responses that we needed were not reported; therefore, these studies were not included in the final list of the systematic review. Many other studies on cardiac amyloidosis had to be excluded because they did not fulfill the strict selection criteria.

#### ***Current Status of AL-CA Treatment Research***

Ongoing clinical trials are evaluating the safety and efficacy of newly developed directed monoclonal antibodies,

which might hold promise for treating AL-CA. Two ongoing clinical trials are evaluating the safety and efficacy of adding CAEL-101, a monoclonal antibody that removes AL amyloid deposits, to standard therapy in AL amyloidosis (NCT04512235 and NCT04304144)

#### ***Strengths and Limitations, and Recommendations for Future Research***

Our study has several strengths. First, this is the first systematic review to the best of our knowledge to synthesize evidence from published studies about the efficacy of different treatment lines for AL-CA. Second, we performed an extensive literature search of multiple databases, and we hand-searched references of the relevant studies for potential articles to be included in the review. Third, we conducted this systematic review in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*, and we reported this article according to the standard reporting guidelines of the PRISMA checklist.

Our study has some limitations. First, the relatively small number of included studies limits the strength of the final conclusions. Second, a lack of standardization in the treatment approach and the lack of standardized outcome measures to indicate successful disease management meant that a meta-analysis could not be conducted. Some studies relied on the hematologic response. Other studies focused on the organ response, namely improvement of cardiac symptoms and/or left ventricular function and wall thickness. Others examined the survival and mortality rates in the population. Third, most of the included studies were retrospective case series. Fourth, most prospective studies were single-arm trials that lacked a standard-treatment comparison arm. This could be justified by the lack of standard guidelines for the treatment of AL-CA, but the fact that investigators used multiple treatment options in their studies meant that multiplicity concerns remain.

Based on these limitations, we see an urgent need for future well-designed, large RCTs to assess the safety and efficacy of AL-CA treatments. Moreover, a uniform primary endpoint should be chosen in clinical trials for AL-CA treatments. These RCTs would be the most efficient way of identifying the optimal strategy for AL-CA management.

#### **Conclusions**

Current evidence suggests several possible regimens for the treatment for AL-CA. Induction therapy with bortezomib-based or dara-CyBorD combinations followed by HDM and ASCT is feasible and well-tolerated. Given the abundant retrospective and single-arm trial data available already, we strongly recommend RCTs to provide evidence about the optimum regimen for AL-CA.

## Disclosures

Dr Hashmi has received funding from Mallinckrodt, Pfizer, Novartis, and Janssen, and travel grants from MSD, Takeda, Gilead, and BMS. None of the other authors declare any relevant conflicts of interest.

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