

# Treatment Options For Relapsed/refractory Systemic Light-Chain (AL) Amyloidosis: Current Perspectives

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**Abstract:** Systemic immunoglobulin light chain (AL) amyloidosis is a disorder characterized by the production of clonal serum free light chains that misfold, aggregate, and deposit in vital organs. Treatment of this disease is typically targeted at the abnormal plasma cell clone in the bone marrow which is the source of the amyloidogenic light chain. First-line therapies in this disease are well established, but in the relapsed or refractory setting, there are many treatment options, including immunomodulatory agents, proteasome inhibitors, alkylating agents, and monoclonal antibodies. Decisions regarding treatment choice should be made by a multidisciplinary team with consideration of the patient's functional status, disease stage, degree of organ dysfunction, and potential treatment toxicities. Herein we review the current treatment options available for patients with relapsed or refractory AL amyloidosis.

**Keywords:** AL amyloidosis, light chain amyloidosis, relapsed, refractory

## Introduction

Systemic immunoglobulin light chain (AL) amyloidosis is a disorder characterized by the production of clonal light chains that misfold, aggregate, and deposit in vital organs. In this life-threatening disease the source of the amyloidogenic light chains is typically a population of clonal plasma cells in the bone marrow and therapy is directed at this abnormal plasma cell clone. The goal of treatment is to suppress or eliminate the clonal plasma cells in an effort to halt further production of amyloidogenic light chains, prevent deterioration in organ function owing to deposition of amyloid fibrils, and to allow organ recovery. The most common organ affected by systemic AL amyloidosis is the kidneys, followed closely by the heart, which is the main determinant of survival and the basis for staging in this disease. Patients with early stage disease will likely survive for many years, however those with advanced cardiac disease, such as Stage III or Stage IIIB, have a limited median overall survival that is approximately 14 months and 5 months, respectively.<sup>1</sup>

Due to the variety of clinical presentations, owing to different degrees of organ involvement, therapy must be tailored to each specific patient based on performance status, organ involvement, and disease stage. Patients with AL amyloidosis often have multi-system organ dysfunction and treatment decisions should be made with input from an experienced multidisciplinary team. In those patients with adequate performance status and organ reserve initial treatment generally includes high-dose

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melphalan and autologous stem cell transplantation (HDM/SCT), melphalan with dexamethasone, or cyclophosphamide/bortezomib/dexamethasone (CyBorD).<sup>2-4</sup>

The majority of patients treated with these therapies will achieve a hematologic response, but despite treatment, most patients will develop disease progression. Hematologic progression is defined by the reappearance of a detectable monoclonal protein or abnormal serum free light-chain ratio after having achieved a hematologic complete response or a 50% increase in serum M protein or urine M protein to >0.5 g/dL or >200 mg/day, respectively, or a free light-chain increase of 50% to >100 mg/L in those with stable disease or partial response.<sup>5</sup> The median time to hematologic relapse is not known for all available therapies, but the time to hematologic relapse after HDM/SCT has been reported by multiple centers with a median of 2 to 4.3 years overall.<sup>6,7</sup> The optimal timing for initiating additional therapy after hematologic relapse is unknown,<sup>8,9</sup> but it is clear that if there is evidence of worsening organ dysfunction then treatment is indicated. Additionally, although most patients achieve a hematologic response to initial therapy, some patients will require a change in therapy to treat refractory disease.

## Proteasome Inhibitors

For those patients with disease that relapses after initial HDM/SCT or who did not receive treatment with a proteasome inhibitor as first-line therapy, bortezomib is often the treatment of choice at the time of first relapse. Bortezomib, the first-in-class proteasome inhibitor, is currently used in the treatment of multiple diseases, including AL amyloidosis in the upfront and relapsed setting. Bortezomib has been proven to be effective as a single-agent in a phase 1/2 trial of 70 patients treated with both once-weekly 1.6 mg/m<sup>2</sup> or twice-weekly bortezomib 1.3 mg/m<sup>2</sup> for relapsed AL amyloidosis. The hematologic response rates in these two groups were 68.8% and 66.7%, respectively, with a median overall survival of 62.1 months and not reached.<sup>10</sup> Kastritis, et al also reported the success of the combination of bortezomib 1.3 mg/m<sup>2</sup> twice weekly with dexamethasone with a response rate of 94% in a group of treatment naïve and relapsed patients with 44% of patients achieving a hematologic CR.<sup>11</sup> A later manuscript including 94 patients (81% with relapsed or refractory disease) demonstrated a hematologic response in 72% (n =67) of evaluable patients with bortezomib doses ranging from 0.7 mg/m<sup>2</sup> twice weekly to 1.3 mg/m<sup>2</sup> once or twice weekly.<sup>12</sup> Additionally CyBorD, previously reported to have high response rates in treatment naïve patients,<sup>3</sup> is also an active regimen in relapsed

disease. For example, one retrospective review included 17 patients with newly diagnosed and relapsed disease treated with CyBorD with a 94% response rate and 71% of patients achieving a hematologic CR.<sup>13</sup> Although the dose of bortezomib used in these trials is varied the most commonly accepted dosing is 1.3 mg/m<sup>2</sup> once weekly based on similar hematologic response rates with once or twice weekly dosing.<sup>14</sup> Additionally for this patient population in which many patients have pre-existing neuropathy, subcutaneous administration of bortezomib is typically recommended due to the lower risk of peripheral neuropathy compared with intravenous administration.<sup>15,16</sup> Overall, bortezomib-based therapies are generally well tolerated in AL amyloidosis and are an excellent choice for second-line therapy, although patients should be monitored for worsening heart failure, hypotension, and peripheral neuropathy.

Carfilzomib, a second-generation irreversible proteasome inhibitor, has not been as readily used in relapsed/refractory AL amyloidosis due to the known cardiac adverse events that have occurred in patients with multiple myeloma, although recent data report that in some cases carfilzomib may be a reasonable treatment option with close cardiac monitoring. Preliminary data from a Phase 1/2 study of carfilzomib with 28 patients with relapsed/refractory disease showed the maximum tolerated dose to be 36 mg/m<sup>2</sup> twice weekly (after initial 20 mg/m<sup>2</sup> dosing).<sup>17</sup> Patients in this trial had a 63% hematologic response rate. Grade 3 or 4 adverse events occurred in 71% of patients with multiple cardiac events, including hypotension, hypertension, decreased ejection fraction, and symptomatic ventricular tachycardia. At the time of data publication, 11 patients had worsening of NT-proBNP on carfilzomib, with 5 of those patients developing progressive cardiac dysfunction. For this reason, although carfilzomib remains an option for treatment of AL amyloidosis, it should be used with extreme caution and with close monitoring of cardiac function in select patients.

The third proteasome inhibitor that was developed, ixazomib, received the Food and Drug Administration breakthrough therapy designation for the treatment of relapsed AL amyloidosis in 2014.<sup>18</sup> Since that time a phase 1/2 study including 27 patients with relapsed or refractory disease was reported.<sup>19</sup> In this study, the maximum-tolerated dose was determined to be 4 mg once weekly and dexamethasone 40 mg on Days 1–4 was added to the treatment regimen if a partial response was not achieved after three cycles. The overall hematologic response rate in this trial was 52% in those treated with the maximum-tolerated dose and the median hematologic progression-free survival was 14.8 months.

The most common adverse events included nausea, diarrhea, fatigue, and skin/subcutaneous tissue disorders. Based on these data a phase 3 trial (NCT01659658) was then initiated comparing ixazomib with dexamethasone to standard therapy. This trial did not demonstrate a significant improvement in overall hematologic response rates and therefore the trial was discontinued after a planned interim analysis was performed.<sup>20</sup>

## Immunomodulatory Agents

In the relapsed setting if a patient has already been treated with proteasome inhibitors then immunomodulatory agents are the most commonly chosen treatment. Thalidomide, the first of the immunomodulatory agents, was previously reported as a treatment option<sup>21,22</sup> although the use of this drug has fallen out of favor due to the availability of the better-tolerated lenalidomide and pomalidomide which do not have the same toxicities reported with thalidomide.<sup>23,24</sup>

Lenalidomide has been studied as a single agent, in combination with steroids and with alkylating agents in relapsed AL amyloidosis and it has demonstrated significant activity in relapsed disease. An initial phase 2 trial included 23 newly diagnosed and previously treated patients.<sup>25</sup> Patients were treated with lenalidomide 25 mg with the addition of dexamethasone if no hematologic response occurred. In this trial, 10 patients discontinued treatment within the first 3 cycles. Hematologic response rate was 41% overall and in those patients that received the combination of lenalidomide and dexamethasone the hematologic response rate was 75%. Myelosuppression, fatigue and rash were the most common adverse events. Another phase 2 trial that enrolled 34 patients (91% of patients had prior therapy) confirmed that the standard lenalidomide dose of 25 mg which is generally used in multiple myeloma was poorly tolerated, but a dose of 15 mg per day had acceptable toxicity and good hematologic responses.<sup>26</sup> This dose, along with concomitant dexamethasone, led to an overall hematologic response rate of 67%, with 29% of patients achieving a complete response. The median time to hematologic response was 6 months. Fatigue and myelosuppression were the most common drug-related adverse events. More recent data in patients with relapsed/refractory disease showed an overall response rate of 61% in a retrospective review of 84 patients with an average time to response of 3 months.<sup>27</sup> Despite these positive results patients should be monitored closely during treatment, as renal dysfunction has been reported in 66% of patients treated with lenalidomide.<sup>28</sup>

Additionally, paradoxical increase in cardiac enzymes has been reported during lenalidomide therapy. An increase of >30% in the B-type natriuretic peptide has been reported to occur in up to 86% of patients receiving lenalidomide and dexamethasone.<sup>29</sup> This increase in BNP can make cardiac response assessment during treatment challenging.

Lenalidomide can also be used in combination with other therapies, most commonly with cyclophosphamide. Two clinical trials have reported on the use of this three-drug combination therapy in a mixed population of newly diagnosed and previously treated patients.<sup>30,31</sup> These trials by Kastritis, et al and Kumar, et al enrolled 37 and 35 patients, respectively, and the overall hematologic response rates were 55% and 60%. The most common adverse events included hematologic toxicity, fatigue, rash, gastrointestinal symptoms, and edema. Another phase 2 trial included 21 patients who were all previously treated and had a hematologic response rate of 62%, with one patient achieving a CR and 5 patients with a very good partial response.<sup>32</sup> Serious adverse events included hematologic toxicity, edema, rash, and renal dysfunction.

For those patients that have persistent disease after treatment with lenalidomide, or have high risk of renal dysfunction, the newer immunomodulatory drug pomalidomide can be used. The efficacy of pomalidomide with dexamethasone was demonstrated in a phase 1/2 trial that enrolled 27 patients with previously treated disease.<sup>33</sup> The maximum-tolerated dose was 4 mg administered with weekly dexamethasone 20 mg. Overall response rate was 50%, time to best hematologic response was 3 cycles, and median response duration was 15 months. Most common drug-related adverse events included myelosuppression and fatigue, with 33% of patients with worsening of renal function as demonstrated by worsening of serum creatinine level. None of the patients required dialysis. Similar results were also reported in another phase 2 trial which enrolled 33 patients.<sup>34</sup> These patients were treated with pomalidomide 2 mg with dexamethasone 40 mg once weekly. Overall hematologic response rate was 48% with a median time to response of 1.9 months. Both of these aforementioned trials reported a similar rise in BNP or BT-proBNP as was seen with lenalidomide therapy. Very similar results were reported by Palladini, et al with a 68% hematologic response rate and a median of 116% increase in NT-proBNP when pomalidomide 4 mg was given in combination with dexamethasone 20 or 40 mg.<sup>35</sup>

## Stem Cell Transplantation

High-dose melphalan and autologous stem cell transplantation are typically used as first-line treatment, although

only approximately 25% of patients will receive this aggressive treatment as it should only be recommended in the setting of preserved functional status and limited organ involvement. For those who are unable to have HDM/SCT at the time of diagnosis, there is also a role for autologous stem cell transplantation in relapsed or refractory disease. In the setting of persistent disease after initial bortezomib-based therapy, HDM/SCT may allow for deeper hematologic responses, improved organ responses, and improved overall survival.<sup>36</sup> Additionally, organ recovery after initial therapy may allow a patient that was initially ineligible for stem cell transplantation to become a candidate for HDM/SCT as demonstrated in one retrospective study of 28 transplant ineligible patients treated with CyBORd or bortezomib/dexamethasone in which 33% of patients became transplant eligible after initial therapy and ultimately were able to undergo treatment with HDM/SCT.<sup>37</sup>

In addition to the use of HDM/SCT after initial non-transplant therapy, there are data that one-third of patients can achieve a hematologic complete response if given a second treatment with HDM/SCT, either 140 mg/m<sup>2</sup> or 200 mg/m<sup>2</sup>.<sup>38</sup> These data showed no treatment-related mortality, but significant grade three and four non-hematologic toxicities, with 73% of patients (n = 8) having relapsed disease within 3 years of the second stem cell transplant. For these reasons, a second treatment with HDM/SCT is not routinely recommended as second-line therapy.

## Alkylating Agents

Another therapy that can be used in relapsed or refractory disease is oral melphalan and dexamethasone. This regimen was reported in a trial of 259 newly diagnosed patients, not eligible for HDM/SCT, treated with melphalan 0.22 mg/kg and dexamethasone on days 1–4 with a hematologic response rate of 76% in the full dose dexamethasone group (40 mg) and 51% in the attenuated dexamethasone group (20 mg).<sup>2</sup> Median overall survival was 7.4 years in the full-dose group and 20 months in the lower dose dexamethasone group. Additionally, melphalan and dexamethasone have been used in combination with bortezomib in newly diagnosed patients with a response rate of 81%.<sup>39</sup> Although melphalan has not been formally studied for use in relapsed patients, its use has been reported in relapsed disease in retrospective reviews.<sup>40</sup>

Successful treatment of patients with AL amyloidosis using bendamustine, another alkylating agent typically used in the treatment of lymphoma, has been reported.

Retrospective data have been published from 122 patients (12 newly diagnosed and the remainder with relapsed or refractory disease) treated with reduced dose bendamustine (<90 mg/m<sup>2</sup>) or standard dose (≥90 mg/m<sup>2</sup>). Overall hematologic response rate was 35% with no difference in OS (p=0.053) or PFS (10 v 8 months, p =0.323) between the two groups. Grade 3 or 4 adverse events occurred in 26% of patients, again without a difference in the 2 groups (p=0.226). Some responses were even seen in patients with disease that was refractory to proteasome inhibitors and imids.<sup>41</sup> Additionally, updated data from a 31 patient phase 2 study of bendamustine and dexamethasone were recently reported<sup>42</sup> In this trial patients with relapsed or refractory disease were treated with 100 mg/m<sup>2</sup> on Day 1 and 2 of each 28-day cycle with 20–40 mg dexamethasone given weekly. Of the 29 evaluable patients, 50% achieved a partial response or better with a median time to best response of 2.7 months (range, 0.9–7.5). The most common adverse events were gastrointestinal symptoms, fatigue, leukopenia, and anemia.

## Monoclonal Antibodies

For those patients previously treated with proteasome inhibitors, immunomodulators, and alkylating agents or for those who are unable to tolerate the side effects of the aforementioned treatments a monoclonal antibody may be a reasonable treatment option. Daratumumab, a CD38 monoclonal antibody that is FDA approved for the treatment of multiple myeloma, has been recently reported to achieve good hematologic responses in AL amyloidosis. Initial data regarding the use of daratumumab were from two cases in which the patients achieved a complete hematologic response.<sup>43</sup> This was followed by a publication describing a retrospective cohort of 25 previously treated patients that received daratumumab.<sup>44</sup> In this cohort, 76% of patients achieved a hematologic response with 36% having a complete response. Since that time data from another retrospective study have been reported with 32 patients, showing a hematologic response rate of 72%.<sup>45</sup> In 2018 preliminary data were presented from the first two prospective trials using daratumumab, which included a trial by Sanchorawala, et al with 12 patients having begun the planned 24 cycles of daratumumab.<sup>46</sup> Ten of the 12 patients achieved a very good partial response with one dose of daratumumab and there were no Grade 3 or 4 infusion reactions. In the second trial, by Roussel et al, updated data shows that 38 patients have enrolled to receive the specified 6 months of daratumumab with an overall

response rate of 59% after one cycle of treatment and 11 patients having a grade 1 or 2 infusion reaction.<sup>47</sup> Although this treatment appears to be well tolerated, data from these reports highlight the need for appropriate pre and post-infusion medications to prevent infusion reactions and close monitor due to reports of increased infection risk in patients receiving daratumumab.

Based on these encouraging data using single-agent daratumumab, this monoclonal antibody has now been used as part of combination regimens in AL amyloidosis, as is typically done in multiple myeloma. A retrospective study was recently published which included 44 patients treated with daratumumab after a median of three prior therapies.<sup>48</sup> One half of these patients received daratumumab as monotherapy and one half received treatment in combination with pomalidomide, lenalidomide, or bortezomib. The overall response rate in this review was 78% in those receiving monotherapy and 88% in those receiving combination therapy. Most responses were very good partial responses or better. Despite most patients tolerating the treatment well, patients receiving combination therapy should be monitored closely, as there was concern for infusion-related reactions and cytopenias occurring more frequently in those patients. Further data regarding the safety of combination therapies with daratumumab will soon be available as the fully accrued trial of daratumumab in combination with CyBORd in newly diagnosed patients will soon be reported (NCT03201965).

Isatuximab, another CD38 monoclonal antibody that is currently being developed for the treatment of multiple myeloma is also being studied in patients with relapsed AL amyloidosis. A phase 2 trial (NCT03499808) has recently completed accrual and will hopefully determine if this is an effective and well-tolerated treatment in AL amyloidosis.

## IgM-Related Amyloidosis

Approximately 4-6% of patients with AL amyloidosis have an underlying IgM paraprotein associated with a lymphoplasmacytic bone marrow clone. Many of the same treatment regimens can be used with good success in these patients.<sup>49</sup> Overall response rate to bortezomib is approximately 82%, immunomodulatory agents have a response rate of approximately 75%, and alkylating agents such as melphalan or cyclophosphamide have response rates of approximately 63%. HDM/SCT is not frequently used in indolent lymphomas in the absence of AL amyloidosis, but the response rate in patients with AL amyloidosis and concurrent lymphoma has been reported as high as

100%.<sup>49</sup> Despite these high overall response rates, the rates of complete response and very good partial responses are much lower and therefore other regimens that may be more effective in indolent lymphomas are often considered. Multiple reports have described the use of combination regimens including the CD20 monoclonal antibody, rituximab, and/or the alkylating agent, bendamustine, which may also be effective in this subset of amyloidosis patients owing to the presence of an underlying lymphoplasmacytic clone.<sup>50,51</sup> Despite the success of these therapies, not all lymphoma therapies will be well tolerated in patients with amyloidosis, as demonstrated by the recent publication describing the poor responses and tolerability of ibrutinib in patients with IgM-related AL amyloidosis.<sup>52</sup>

## Anti-Fibril Agents

In recent years the focus of treatment in AL amyloidosis, both in newly diagnosed and relapsed/refractory disease, has also turned towards elimination of amyloid deposits in an effort to improve the function of organs already affected by amyloid deposition. The development of this type of targeted therapy has thus far been limited to NEOD001, CPHPC, and CAEL-101. NEOD001, a humanized form of murine monoclonal antibody 2A4, that was developed to bind to the misfolded light chain was first reported to have positive effects in 2014 in a trial of 27 patients with relapsed/refractory disease. It was shown that monthly infusions of NEOD001 were well tolerated and safe with 57% of patients having cardiac response and 60% with renal response.<sup>53</sup> The development of this drug was ultimately halted after the phase 2b trial, PRONTO (NCT02632786), did not meet its primary or secondary endpoints and the then ongoing phase 3 VITAL trial (NCT02312206) was stopped after futility analysis. Initial data for the use of CPHPC, a small molecule that binds circulating serum amyloid P (now called miridesap), in combination with an IgG anti-serum amyloid P antibody showed clearance of amyloid deposits in an initial 15 patient phase 1 clinical trial.<sup>54</sup> This combination was then pursued in phase 2 nonrandomized trial (NCT03044353) which has since been halted due to serious adverse events and the development of this therapy has also ceased. Currently, CAEL-101, a chimeric monoclonal antibody that targets amyloid fibrils, is the only anti-fibril agent that remains in development. Data supporting development of this drug comes from an initial phase 1a/b clinical trial that showed an organ response in 66% (12 of 18) of evaluable patients with cardiac or renal disease.<sup>55</sup> It is expected that clinical trials with this agent will be opening in the near future.

## Novel Therapies And Ongoing Clinical Trials

Additional therapies are currently being explored in relapsed amyloidosis, including the use of anti-apoptotic therapies which target BH3 family proteins. One such example, venetoclax, is a BCL-2 inhibitor which has been reported to be effective in some cases of multiple myeloma, with an overall response rate of 21% in all relapsed/refractory patients, but a 40% response rate in those patients with a t(11;14).<sup>56</sup> In combination with bortezomib and dexamethasone, the response rate increased to 67% in a small phase 1b trial in multiple myeloma.<sup>57</sup> Translocation (11;14) is a common chromosomal abnormality in multiple myeloma, although it only occurs in 15–20% of patients and is considered a standard risk mutation.<sup>58,59</sup> Conversely, this mutation is present in approximately 50% of patients with AL amyloidosis<sup>60</sup> and has been reported to confer resistance to bortezomib based on data that show a worse event-free survival (HR 2.94; 95% CI 1.37–6.25,  $p=0.006$ ) and OS (HR 3.13; 95% CI 1.16–8.33,  $p=0.03$ ) in those with the mutation.<sup>61</sup> Treatment outcomes of patients with AL amyloidosis, in particular, those with t(11;14), may be improved by the use of venetoclax as monotherapy or in combination with other therapies. Multiple case reports and a small case series have demonstrated efficacy of this treatment in select patients, with a limited number of patients achieving sustained hematologic responses and one patient also achieving organ responses.<sup>62–64</sup> Despite these initial positive reports, more data are needed to evaluate the efficacy of this treatment in patients with and without t(11;14).

Currently, there are multiple ongoing clinical trials for patients with previously treated AL amyloidosis. Enrollment is occurring in trials with lenalidomide, dexamethasone, and elotuzumab (NCT03252600) and daratumumab, ixazomib, and dexamethasone (NCT03283917). Additional trials using other novel agents, such as venetoclax are currently in development.

## Conclusion

Unfortunately, despite the many therapeutic options available for AL amyloidosis, it remains a devastating disease that is life-threatening in the majority of cases. Patients with this disease often present with severe organ dysfunction and treatment decisions, as well as supportive care decisions, should be made by a multi-disciplinary team keeping in mind the individual patient's organ involvement, symptoms, and functional status. Although current options for relapsed disease include alkylating agents,

proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies, additional better-tolerated therapies are desperately needed to treat those patients with severely advanced disease and to also treat those patients with multiply relapsed or refractory disease.

## Disclosure

The authors report no conflicts of interest in this work.

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