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Review

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Current Updates on the Management of AL Amyloidosis

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Abstract

Systemic immunoglobulin light chain (AL) amyloidosis is a rare but fatal disease. It results from clonal proliferation of plasma cells with excessive production of insoluble misfolded proteins that aggregate in the extracellular matrix, causing damage to the normal architecture and function of various organs. For decades, treatment for AL amyloidosis was based mainly on therapeutic agents previously studied for its more common counterpart, multiple myeloma. As the prevalence and incidence of AL amyloidosis have increased, ongoing research has been conducted with treatments typically used in myeloma with varying success. In this review, we focus on current treatment strategies and updates to clinical guidelines and therapeutics for AL amyloidosis.

Keywords: AL amyloidosis; Light chain amyloidosis; AL amyloidosis therapy; Light chain amyloidosis treatment

Introduction

Immunoglobulin light chain (AL) amyloidosis is a rare disease characterized by clonal proliferation of plasma cells with over-production of monoclonal light chains that transform into misfolded protein fibrils, with a special configuration making them insoluble and causing large-scale depositions in the extracellular matrix resulting in organ dysfunction. AL deposits most commonly accumulate in the heart and kidneys but can affect other organs, including the peripheral nervous system. This process results in cytotoxicity and ultimately organ dysfunction [1]. Though AL amyloidosis prevalence in the USA is low (40.5 cases per million in 2015) [2], the mortality rate is high, with an average survival ranging 6 - 36 months [3, 4]. AL amyloidosis can affect multiple organs either simultaneously or separately and can manifest with a wide variety of non-specific presenting symptoms, e.g., unexplained heart failure, heavy proteinuria, hepatomegaly, or neuropathy. This heterogeneity of presentations makes it difficult to diagnose AL amyloidosis at earlier stages [5]. The ultimate diagnosis for AL amyloidosis requires tissue and/or bone marrow biopsy confirmation in addition to an extensive laboratory and imaging workup (Table 1) [6], which might cause further delay for the diagnosis [7]. Based on observations from the clinical trials, prognostic factors for risk stratification formulate an individualized treatment plan for each patient and predict morbidity and mortality [6, 8, 9]. It is important to mention that the burden of cardiac involvement is the most important prognostic factor for the treatment outcome and overall survival (OS).

Currently, there are no clear guidelines on systemic AL amyloidosis treatment [10]; however, since both AL amyloidosis and multiple myeloma (MM) are monoclonal plasma cell dyscrasias, AL amyloidosis treatment strategies and medications are derived from the anti-plasma cell therapy that is used for MM [11]. Interestingly, lower tumor burdens and cytogenetic abnormalities are associated with better treatment outcomes in AL amyloidosis than in MM [12]. Therapy is aimed at achieving deep and rapid hematological response, which reverses amyloid-mediated organ dysfunction, and improves OS [13-15]. Table 2 [9, 16-44] summarizes therapeutic combinations in the management of AL amyloidosis.

Autologous Stem Cell Transplantation (ASCT)

ASCT with high-dose melphalan conditioning was first described in the literature as a treatment for AL amyloidosis in 1998 [45]. The only randomized controlled trial evaluating the efficacy of ASCT in AL amyloidosis was published in 2007 and compared patients treated with high-dose melphalan followed by ASCT to those who received melphalan and dexa-

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Table 1. Diagnostic Workup for AL Amyloidosis

1) Serum and urine electrophoresis with immunofixation
2) Serum free light chain assay
3) Complete blood count
4) Comprehensive metabolic panel including liver and renal function
5) Troponin T level
6) NT-proBNP level, BNP level
7) 24-h urinary protein with immunofixation
8) Creatinine clearance
9) Factor X level
10) Bone marrow aspirate and biopsy with FISH studies
11) Bone imaging (if multiple myeloma is suspected)
12) Cardiac involvement assessment: echocardiogram, magnetic resonance imaging
13) Abdominal ultrasonography
14) EMG/nerve conduction study if suspected neuropathy
15) Fat pad biopsy, Congo red stain, mass spectrometry
16) Endoscopy and colonoscopy if AL amyloidosis involving gastrointestinal tract is suspected

NT-proBNP: N-terminal prohormone of brain natriuretic peptide; FISH: fluorescence *in situ* hybridization; EMG: electromyography.

methasone (M-D) without ASCT. Median OS in the patients medically managed was significantly improved compared with the group undergoing ASCT (OS 56.9 months versus 22.2 months, P = 0.04) [46]. This result has withstood several criticisms. First, there was a high treatment-related mortality (TRM) in the ASCT arm, but landmark analysis in patients surviving 6 months showed no difference in outcomes among groups. Second, some higher-risk patients were included in the study. However, an analysis of good-risk patients also showed no difference in outcomes at 3 years (58% OS in ASCT versus 80% OS in M-D, P = 0.13). Third, the duration of response of M-D was questioned versus ASCT, which is thought to offer a more durable response. In a long-term follow-up of the data, the results of ASCT versus M-D were again similar [47]. Both medical therapy for AL amyloidosis and ASCT management have improved since this trial. The reduction in TRM of ASCT in the modern era is primarily due to improved peri-transplant care and better patient selection, including the incorporation of cardiac biomarkers [48]. Due to the commonly late diagnosis of AL amyloidosis, only 20% of patients are found to be eligible for ASCT therapy at the initial diagnosis [9].

High-dose melphalan followed by ASCT is considered the most commonly used first-line therapy for patients who fit the eligibility criteria for ASCT. Oral chemotherapy induction was not found to be helpful and led to disease progression and disqualification for ASCT in some patients [49]. However, bortezomib-based induction with two cycles prior to ASCT was found to improve hematologic remission and OS in a randomized controlled trial and several retrospective studies [50-52]. Landau et al published a pilot study that involved 19 patients newly diagnosed with AL amyloidosis who underwent three phases of therapy, including an induction phase with bortezomib and dexamethasone (BD) for 1 - 3 cycles, followed by risk-adapted ASCT (the induction dose of melphalan was adapted based on the risk stratifications and organ involvement), and ultimately six cycles of consolidation therapy with BD [53]. OS rate and 2-year progression-free survival (PFS) rate were 84% and 64% respectively, with an overall response rate (ORR) of 91% (37% achieved complete response (CR), 37% achieved very good partial response (VGPR), and 21% achieved partial response (PR)). This regimen furthers the hypothesis that proteasome inhibitors (PIs) like bortezomib have a synergistic effect when used in conjunction with alkylator therapy as apoptotic agents that prevent further clonal plasma cell proliferation and augment the effect of ASCT [54, 55]. Cornell et al reported a better outcome of induction therapy with bortezomib prior to ASCT in patients with low burden plasma cells (PCs) (PCs $\leq$ 10%) when compared to no induction therapy. Bortezomib was able to lower the relapse/progression events (hazard ratio (HR), 0.43; 95% confidence interval (CI), 0.24 to 0.78; P < 0.01) and prolong the PFS rate at 2 years (HR, 0.43; 95% CI, 0.26 to 0.72; P < 0.01) [56]. According to the latest recommendations from the Mayo Clinic, induction therapy with bortezomib is highly recommended, particularly when bone marrow PCs are $\geq$ 10%, in high-risk cytogenetics (e.g., 17p deletion, t(4;14), t(14;20)), or concurrent myeloma) [16]. In addition, Center for International Blood and Marrow Transplant Research (CIBMTR) registry data showed that patients who received bortezomib-based induction had improved progression ratio, which suggests that pre-transplant bortezomib-based induction is better than proceeding with upfront ASCT. The relevance of minimal residual disease, cytogenetics, and maintenance therapy is being explored.

Regarding melphalan conditioning dose, a higher dose (70 - 200 mg/m^2) preceding ASCT was associated with a better hematological response and increased median OS than a lower dose [17, 18]. Moreover, a high melphalan induction dose of

Table 2. Therapeutic Combinations in the Management of AL Amyloidosis

Treatment	Line of therapy	Description
Autologous stem cell transplant (ASCT)	1) Upfront transplant (in selected cases); 2) Consolidation after induction [16]	1) High-dose melphalan 200 mg/m^2 followed by ASCT is considered as first-line treatment for patients who fit eligibility criteria and have minimum plasma cell percentage (< 10%) in the bone marrow [9, 17, 18]; 2) Criteria for HD-ASCT include patients up to 65 - 70 years of age with estimated glomerular filtration rate (eGFR) > 50 mL/min, low cardiac biomarkers (NT-pBNP < 590 pmol/L and/ or troponin T < 0.06 ng/mL), plasma cell infiltration (< 10%) in the bone marrow at the time of transplant; 3) ASCT should be avoided in patients with severe autonomic neuropathy, significant gastrointestinal bleeding, advanced renal failure over 70 years (case by case basis), amyloid-related symptomatic pleural effusions or poor Eastern Cooperative Oncology Group performance status (> 2) [41]; 4) Bortezomib-based induction therapy is considered prior to ASCT if plasma cells > 10% in the bone marrow.
Alkylating agent (melphalan) and dexamethasone		
Melphalan and Dex (M-Dex)	First-line therapy in selected transplant ineligible patients	Melphalan-dexamethasone can be considered as first line in elderly patients, neuropathy, poor performance status. Complete response (CR) rate 33%, overall response rate (ORR) 67% [19].
Proteasome inhibitior therapy		
Bortezomib	Backbone therapy for various combinations	
Bortezomib, cyclophosphamide, dexamethasone (CyBorD)	First line or relapse AL amyloidosis (can be considered for both transplant eligible and ineligible	CyBorD as upfront or second-line therapy is very effective regimen with overall hematologic response up to 94%. The regimen can be used in both transplant eligible and ineligible patients [20, 21].
Bortezomib, melphalan, dexamethasone (BMDex)	First line or relapse AL amyloidosis (transplant ineligible patients)	Treatment with BMDex compared with MDex resulted in improved hematologic responses at 3 months (79% vs. 52%; P = 0.002), Very good partial response (VGPR) and CR (64% vs. 39%; hazard ratio, 2.47; 95% confidence interval (CI), 1.30 to 4.71). Overall survival (OS) with 50% decrease in mortality rate [22].
Bortezomib, lenalidomide, dexamethasone (VRd)	Use is limited to selected patients with t11:14, no cardiac involvement, no history solid organ transplant	1) The regimen has high rate of VGPR at 6 months compared to CyBorD regimen (92% vs. 61%) [23]. Consider weekly bortezomib, low-dose lenalidomide (5 mg), and weekly dexamethasone; 2) The regimen is not used as upfront due to its non-hematologic toxicity; 3) Combination should be avoided in patients with cardiac involvement.
Carfilzomib	Not recommended outside of clinical trial	Patients have high grade 3 and grade 4 cardiac, renal, pulmonary and hematologic toxicities.
Ixazomib		
Ixazomib + dexamethasone	Relapse/refractory AL amyloidosis after one or more prior lines of therapy	1) Hematologic response are 52%, 1-year OS 85% [42]; 2) Phase 3 ongoing, NCT01659658
Ixazomib + cyclophosphamide + dexamethasone	Investigational	Phase 1/2 ongoing in patients with relapse AL amyloidosis (NCT01864018, NCT03236792)

Table 2. Therapeutic Combinations in the Management of AL Amyloidosis - *(continued)*

Treatment	Line of therapy	Description
Immunomodulatory drugs		
Thalidomide		
Thalidomide, dexamethasone	1) Rarely used due to toxicity; 2) Not commonly prescribe in USA	1) Hematologic response 48%, CR 15%; 2) Increase risk of symptomatic bradycardia [24]
Thalidomide, cyclophosphamide, dexamethasone	1) Use in relapse AL amyloidosis (case by case basis); 2) Not commonly prescribe in the USA	1) Hematologic response 74%, CR 21% [25]; 2) Increase risk of cardiotoxicity
Lenalidomide		
Lenalidomide-dexamethasone	Limited to selected cases for both first line and relapse AL amyloidosis	1) Hematologic response 61%, CR 20% [26]; 2) Serious cardiac and renal toxicity are reported [27, 28].
Lenalidomide, cyclophosphamide, dexamethasone	Limited to selected cases for both first line and relapse AL amyloidosis	1) Hematologic response 60%, VGPR 40% in upfront treatment; 2) Higher rate of hematologic toxicity [43]
Pomalidomide		
Pomalidomide-Dexamethasone	1) Preferred over lenalidomide and dexamethasone; 2) Use is limited to relapse AL amyloidosis	Overall hematologic response varies 48-68% in relapse AL amyloidosis. Rapid response can be seen after starting treatment [29, 30].
Monoclonal antibodies targeting CD38		
Daratumumab (IV)	Heavily pretreated AL amyloidosis	1) Hematologic response is 76%, CR 36%, VGPR 24%; 2) Median hematologic response reported at 1 month [31]
Daratumumab (SQ), bortezomib, cyclophosphamide, dexamethasone	Recommended as first line induction therapy both in transplant eligible and transplant ineligible patients (preferred)	1) Overall hematologic response reported 92%, CR 53% compared to CyBorD alone (77%, CR 18%) [32, 33]; 2) Six-month cardiac response 42% versus 22%; 3) Six-month renal response 54% versus 27%
Ixazomib + daratumumab + dexamethasone	Investigational	Combination is currently investigated in heavily pretreated AL amyloidosis (NCT03283917).
Daratumumab, pomalidomide	Investigational	Combination is currently investigated in heavily pretreated AL amyloidosis (NCT04895917).
Isatuximab	Investigational	Preliminary phase 2 results showed hematologic response 77%, VGPR 54% (NCT 08399808) [44].
Targeting amyloid component therapy		
NEOD001	Investigational	Clinical trial failed to prove significant improvement in outcomes. Subgroup analysis of VITAL suggests benefit in Mayo stage IV patients with severe cardiac involvement and confirmatory trial is planned [34].

Table 2. Therapeutic Combinations in the Management of AL Amyloidosis - *(continued)*

Treatment	Line of therapy	Description
CAEL-101	Investigational	1) 63% patients have organ response [35, 36]; 2) A double-blind, randomized, multicenter international phase 3 study of CAEL-101 combined with the SoC treatment for plasma cell dyscrasia (PCD) versus placebo in patients with treatment naive Mayo stage IIIb AL amyloidosis (NCT045004825); 3) A phase 3, double-blind, multicenter study to evaluate the efficacy and safety of CAEL-101 and plasma cell dyscrasia treatment versus placebo and plasma cell dyscrasia treatment in plasma cell dyscrasia treatment naive patients with Mayo stage IIIa AL amyloidosis (NCT04512235).
Anti-metabolite and alkylating agent		
Bendamustine	Investigational	Has better hematologic response in relapse IgM AL amyloidosis compared to non-IgM AL amyloidosis (58% versus 28%) particularly in combination with rituximab [37]
Small molecules		
Doxycycline	Consider doxycycline as an adjuvant to standard chemotherapy	Doxycycline is associated with better hematologic response and survival rates at 12 and 24 months compared to matched historical controls (82% versus 53%), and (82% versus 40%) [38]
Venetoclax (BCL-2 inhibitor)	Investigational	Drug is evaluated as single agent and in combinations. Venetoclax has shown promising results with t11:14 translocation. Despite biochemical response, safety concerns and increase risk of death is a concern which require further investigation before its use to patients.
Epigallocatechin-3-gallate (ECGC)	Investigational	Use as an adjuvant treatment is not well established [39, 40].
Ibrutunib (bruton tyrosine kinase (BTK) inhibitor)	Investigational	Ibrutinib with or without bortezomib and dexamethasone in treating patients with relapsed or refractory immunoglobulin light chain amyloidosis (NCT03130348)
Oncopeptides		
Melflufen + dexamethasone	Investigational	A phase 1/2 open label study of melphalan flufenamide (melflufen) in combination with dexamethasone for participants with Al amyloidosis following at least one prior line of therapy (NCT04115956)

200 mg/m^2 was tolerable in patients above the age of 65 with good performance status (Karnofsky Performance status scale of ≥ 90) with no increase in TRM except for a noticeable increase in post-transplant febrile neutrophilia and infections [57]. Low-dose melphalan is used in MM for patients with dialysis-dependent end-stage renal disease (ESRD) with similar efficacy and TRM as melphalan 200 mg/m^2 [58]. However, no studies have yet investigated similar approaches in patients with AL amyloidosis.

Consolidation therapy consists of treatment with any therapeutic agent against PCs initiated post-ASCT to maintain or deepen the response of the ASCT; it is usually reserved for patients with more advanced disease stages who failed to achieve a favorable outcome with ASCT therapy. Interestingly, consolidation therapy was found to achieve a better PFS rate and median OS in patients with less than VGPR (22.4 and 125.8 months, respectively) compared to patients with VGPR or better (8.8 and 74.4 months, respectively) [59]. Routine maintenance therapy may not be of benefit, as lenalidomide failed to demonstrate any difference in the mean OS or PFS rate after ASCT in this setting [60].

Though acquired factor X deficiency is not as common in AL amyloidosis as it is in MM, it is associated with a worse outcome with a lower median OS (associated with a median OS of 9.3 months vs. 118.4 months in patients without factor X deficiency) [61]. It is important to note that severe factor X deficiency (< 25% deficiency) was associated with a higher incidence of serious bleeding complications in the peri-transplant period, particularly when combined with other factor deficiencies, and it is important to screen patients with AL amyloidosis for factor X deficiency before offering them ASCT [62].

Alkylating Agents and Steroids

Since the first randomized controlled trial in AL amyloidosis in 1978 demonstrated that melphalan and prednisone improve outcomes when compared with placebo, alkylating agents have been used as the mainstay of therapy in this condition [63]. Subsequent studies proved that melphalan and prednisone were superior to colchicine, an anti-inflammatory medication [64]. In a sicker population of patients not eligible for ASCT, Palladini and colleagues in 2007 demonstrated encouraging outcomes with the M-D regimen, of whom 67% were able to achieve a hematological response (CR in 33%) [19]. Even in the prolonged follow-up of the survivors (median follow-up 5 years), the median PFS rate and median OS were 3.8 and 5.1 years, respectively. As noted above, Jaccard et al found that M-D was able to achieve a comparable result and a better TRM profile compared to ASCT [46, 47].

Over time, dexamethasone has replaced prednisone due to stronger glucocorticoid effects and improved survival data in patients with MM [65]. The use of multiple alkylating agents + prednisone was not found to be beneficial versus melphalan + prednisone, suggesting that medications with different and potentially synergistic mechanisms were needed to improve outcomes [66].

Proteasome Inhibitors

The proteasome is a cellular complex that participates in protein degradation, which is considered a vital step in cell growth, maturation, and proliferation [67]. Since the FDA approved the first PI, bortezomib, in 2003, the treatment of PC clonal dyscrasias has greatly advanced [68].

Bortezomib

Bortezomib has been used in AL amyloidosis as a single agent or in combination with other chemotherapeutic agents. A retrospective study of 43 patients received bortezomib in combination with cyclophosphamide and dexamethasone (CyBorD) either as upfront or second-line therapy for relapsed disease and found an overall hematological response of 81.4% with a CR of 39.5%; CR was significantly higher in the upfront therapy group vs. the relapsed group (65.0% vs. 21.7%, respectively; P = 0.003) [20]. Moreover, the 1-year and 2-year PFS rates were better in the upfront group compared to the relapsed group (74.5% vs. 70.9% for 1 year, and 66.5% vs. 41.4% for 2 years, respectively). Similarly, Mikhael et al found a rapid and solid hematological response with CyBorD in both newly diagnosed and relapsed/refractory AL amyloidosis patients (time to response was 2 months, and the hematological response was achieved in 94% of patients), and three patients were later able to have ASCT despite initially being classified as ASCT-ineligible [21]. Subsequently, in 2015, Palladini et al investigated the role of CyBorD based on disease severity in a large retrospective study [69]. A total of 230 patients were classified into stage I, II, or III based on the Mayo Cardiac Staging System (Table 3 [6, 70, 71]), with stage III being further divided into stage IIIa or stage IIIb based on the level of amino-terminal pro-natriuretic peptide type-B (NT-proBNP); stage IIIa was below the value of 8,500 ng/L, and stage IIIb was above this value, which indicates a very poor prognosis. The hematological response varied significantly based on the degree of cardiac involvement with overall response rates of 77%, 64%, 69%, and 42% for stage I, II, IIIa, and IIIb, respectively; CR was 33%, 18%, 23%, and 14%, respectively. The 5-year survival rate for the entire population was 55%. Palladini et al published a case-control trial of M-D versus BMDex and found improved rates of complete hematologic response with the bortezomib-based regimen but no change in OS. This was driven by no survival advantage in patients with severe cardiac disease [72]. Similarly, BMDex was found superior to M-D in improving hematological response and OS rates in a recent phase III multicenter, randomized, open-label clinical trial [22]. Sperry et al studied patients with AL amyloidosis presenting with symptomatic heart failure. They found that the regimen of bortezomib, dexamethasone and an alkylating agent (either cyclophosphamide or melphalan) was associated with improved outcomes when compared with other initial regimens [73].

Bortezomib may also be combined with immunomodulatory drugs (IMiDs), particularly the VRD regimen (bortezomib + lenalidomide + dexamethasone). One study showed a favora-

Table 3. Prognostic Mayo Staging System for AL Amyloidosis 2012

Stage	No. of factors	OS in patients who received ASCT		OS in patients who did not receive ASCT	
		No. of months	% of 4-year survival rate	No. of months	% of 5-year survival rate
Stage I	0	Not reached	87	55	50
Stage II	1	97	72	19	35
Stage III	2	58	56	12	20
Stage VI	3	22	46	5	15

Factors related to risk stratification: 1) NT-proBNP ≥ 1,800 ng/L; 2) cTnT ≥ 0.025 µg/L; 3) FLC-diff ≥ 18 mg/dL. Mayo staging system has three different models, including 2004 and 2004-European staging systems, which do not include FLC-difference as a prognostic factor (they include only NT-proBNP ≥ 332 ng/L and cTnT ≥ 0.035 µg/L). Mayo staging system 2004-European model further classified stage III based on the NT-proBNP of 8,500 ng/L (stage IIIa has the two factors higher than the cutoff point with NT-proBNP < 8,500 ng/L, and stage IIIb has the two factors higher than the cutoff point with NT-proBNP > 8,500 ng/L), which found to be more useful in predicting early death within 6 months from diagnosis compared to other staging systems. Thus, it has been used more in determining patient eligibility for participation in clinical trials and to further stratify patients into intermediate vs. high-risk groups [111]. NT-proBNP: N-terminal prohormone of brain natriuretic peptide; FLC-diff: the difference between involved and uninvolved free light chains; OS: overall survival; ASCT: autologous stem cell transplantation; cTnT: cardiac troponin T.

ble hematological response (75.5% after the first cycle with 88% based on intention to treat analysis) and a trend towards a deeper response when compared with CyBorD [23]. Though, this was at the expense of increased toxicity, particularly skin rashes and other non-hematological adverse events (AEs).

Though it has become a backbone treatment for AL amyloidosis, it is important to note that bortezomib therapy is associated with a resistant and less-favorable outcome in AL amyloidosis patients harboring t(11;14) [74]. The most detrimental adverse effect is neuropathy, which has a greater incidence at higher and more prolonged dosing and when the intravenous form is given instead of the subcutaneous form [75, 76].

Carfilzomib

Carfilzomib is a second-generation PI that selectively inhibits chymotrypsin-like (CT-L) activity, a major driver of enhanced cell death in transformed cells with preservation of the proteasome function in non-transformed cells; this is in contrast to bortezomib, which has non-selective PI properties (CT-L, caspase-like (C-L), and trypsin-like (T-L)) causing cytotoxic effects on malignant and non-malignant cells [77]. Carfilzomib showed a comparable result when used in patients with relapsed-refractory AL amyloidosis. A total of 929 patients with refractory AL amyloidosis were recruited between June 20, 2012 and June 30, 2014; 464 were randomly assigned to receive carfilzomib and dexamethasone (with a median follow-up of 11.9 months), while the rest received BD (with a median follow-up of 11.1 months). Carfilzomib therapy was associated with prolonged median PFS compared to bortezomib therapy (18.7 vs. 9.4 months, respectively) [78]. Despite that, carfilzomib is to be used cautiously in cases of refractory AL amyloidosis because the higher doses were associated with more grade 3-4 toxicities, namely cardiac, renal, pulmonary, and hematological toxicities [78, 79]. The only exception is neurotoxicity; carfilzomib was found to be associated with a lower incidence of neurotoxicity, which may make it a better upfront therapy line for patients who have AL amyloidosis associated with neuropathy in contrast to bortezomib; however, the available data are not sufficient to generalize this hypothesis [80]. In fact, in MM, the carfilzomib-lenalidomide-dexamethasone (KRd) regimen was found to have similar PFS compared to bortezomib, lenalidomide, and dexamethasone (VRd) with more toxicity [81]. Further study of carfilzomib in AL amyloidosis is needed.

Ixazomib

Ixazomib is an oral PI that was approved for relapsed/refractory MM treatment in 2015 [82]. The role of ixazomib in AL amyloidosis is not well studied in clinical trials. Initial data from a clinical trial performed on 27 patients who failed the first-line therapy for AL amyloidosis were positive, with an overall hematological response of 52%, including a documented organ response in 56% of patients; the median PFS and 1-year PFS were 14.8 months and 60%, respectively [42]. However, the TOURMALINE-AL1 trial, a multicenter international phase III clinical trial that was designed to evaluate the role of ixazomib in addition to dexamethasone in 248 patients with refractory/relapsed AL amyloidosis, was terminated because ixazomib failed to achieve a desired hematological response compared to other standard regimens [83]. Currently, ixazomib is under investigation in combination with other chemotherapeutic drugs in both upfront and relapsed disease (NCT03236792, NCT01864018, and NCT03283917) [84]. The promise of an oral PI is enticing, given easier administration and less neuropathic side effects. Though, skin rash appears to be more prevalent with ixazomib.

IMiDs

In order to maintain their accelerated growth, tumor cells secrete cytokines that suppress natural immune responses and prevent tumor antigens' recognition by the immune system. One of the well-known mechanisms by which the tumor microenvironment can escape immune system surveillance is by increasing T-regulatory cells, a group of CD4 T cells. T-regu-

latory cells counteract the normal function of cytotoxic CD8 T cells and natural killer (NK) cells against tumor cells and interfere with their ability to identify tumor cell epitopes. Immunomodulator therapy was found to play a pivotal role in upregulating and modulating this imbalance by co-stimulating CD8 T cells and NK cell production and enhancing their function against tumor cells [85]. Although they achieved a good outcome in MM, IMiDs were associated with higher rates of toxicity in AL amyloidosis patients [86].

Currently, IMiDs are considered second-line therapy in AL amyloidosis [9]. However, they are frequently used as an oral option for maintenance therapy after CR or VGPR has been achieved.

Thalidomide

Thalidomide was initially marketed and developed as a sedative and was used in pregnant women, leading to severe congenital disabilities. It was taken off the market by the FDA in 1961, but subsequent trials in leprosy demonstrated benefit. After its approval in 1998 for this condition, it was tested and showed remarkable benefit on outcomes in MM, leading to its approval for this condition in 2006 [87, 88]. The role of thalidomide role in AL amyloidosis was investigated by Palladini et al [24]. Out of 31 patients who received thalidomide and dexamethasone, 15 patients (48%) were able to achieve a hematological response with CR detected in six patients (19%) with a significant improvement in organ functions. Despite that, only 35% of patients were able to tolerate the full dose of thalidomide because of associated AEs, mainly symptomatic bradycardia (incidence rate of 26%). Adding alkylator-like cyclophosphamide to the previous regimen achieved a hematological response of 74%, including CR in 21% when used in 75 patients with advanced AL amyloidosis [25]. Median OS was 41 months with a 3-year survival rate of 100% in the CR group. TRM was 4%, with 8% of patients experiencing drug toxicity that indicates drug cessation. A slightly better hematological response and CR were observed by Venner et al in 2014 (79.7% and 24.6%, respectively) with substantial concerns related to cardiac toxicity associated with thalidomide therapy [89].

Lenalidomide

Lenalidomide and pomalidomide are associated with a slightly better toxicity profile. Evaluating lenalidomide in combination with dexamethasone (Len-D), particularly in patients with refractory/relapsed disease, did not show consistent results, including one study that showed a total hematological response of 41% only (including 0% CR) [90], and another study that showed a 61% overall hematological response (including 20% CR) [26]. Using lenalidomide as a single agent was associated with a lower efficacy in treating AL amyloidosis [27, 28]. Lenalidomide and dexamethasone have been tested with both alkylators. In a single center prospective clinical trial, using melphalan, lenalidomide and dexamethasone (MLD) in 50 patients newly diagnosed with AL amyloidosis achieved a total hematological response of 68%, including a CR of 18%, with median OS and PFS of 67.5 months and 25.1 months, respectively [91]. Similarly, using a cyclophosphamide, lenalidomide and dexamethasone (CLD) regimen as an upfront therapy in a multicenter prospective clinical trial that included 24 newly diagnosed patients with AL amyloidosis achieved a total hematological response of 46%, including CR in 25% [92]. It is important to note that grade 3-4 AEs may be higher in the MLD regimen.

Pomalidomide

Pomalidomide is another second-generation IMiD approved by the FDA for MM treatment in 2008 [93]. Though the clinical data that support the use of this therapy in AL amyloidosis are based only on phase 1-2 trials, the outcomes are encouraging. A total of 29 patients received pomalidomide between 2009 and 2017 in the UK for AL amyloidosis; only 39% were able to achieve VGPR at 6 months, and no patients achieved CR. However, pomalidomide achieved a rapid response with median OS and PFS of 27 months and 15 months, respectively [94]. On average, the overall hematological response in patients with relapsed/refractory AL amyloidosis who received a combination of pomalidomide and dexamethasone ranged between 48% and 68%, with a very rapid response reported within 1 month [29, 30].

Second-generation IMiDs, particularly pomalidomide, were associated with a favorable outcome in refractory/relapsed AL amyloidosis with a hypothesis that they overcome alkylator/bortezomib resistance in previously treated AL amyloidosis [21, 90]. Pomalidomide and dexamethasone's role in treating relapsing/refractory AL amyloidosis was recently investigated in a retrospective study for 153 patients, where 93% of them previously received bortezomib, 81% lenalidomide, 75% melphalan, and 24% had ASCT [95]. In combination with dexamethasone, pomalidomide was able to achieve an overall hematological response of 44% after six cycles, with an increase in median OS up to 50 months.

It is important to keep in mind that treatment with IMiDs, particularly when used in AL amyloidosis, can be associated with fluid retention and an increase in NT-proBNP. However, it is not clear if this increase is related to the direct cardiotoxic effect of IMiDs or fluid retention, causing an elevation in NT-proBNP [96]. Additionally, as IMiDs can upregulate parts of the immune system, they should not be used in patients after solid organ transplantation due to the risk of precipitating acute rejection [97].

Monoclonal Antibodies Targeting CD38

CD38 is a transmembrane glycoprotein molecule that plays an important role in cell adhesion and is heavily present in clonal PCs [98]. Daratumumab is a humanized monoclonal antibody against CD38 that can initiate antibody-mediated cellular toxicity along with complement-mediated cytotoxicity [99]. After

achieving a satisfactory outcome in treating MM, daratumumab has been used in clinical trials of AL amyloidosis treatment recently, mainly for relapsed/refractory disease. Shortly after being approved by the FDA for refractory/relapsed MM in 2015 [100], the efficacy and safety of daratumumab in AL amyloidosis was investigated in a small case series; daratumumab was able to decrease serum-free light chain levels significantly and rapidly [101]. A multicenter phase II clinical trial AMYDARA recruited 40 patients diagnosed with refractory AL amyloidosis who were previously treated (median of three of therapy, range 1 - 5), with more than 50% of patients having equal to or more than two organs involved [102]. A total of 55% of patients achieved a hematological response, including 47.5% with a VGPR or better. As in the previous case series [101], this prospective study demonstrated a very rapid hematological response in patients treated with daratumumab (median hematological response of 1 week). Adding dexamethasone to daratumumab was associated with a better total hematological response of 76%, including CR in 36% when used in 25 patients with previously treated AL amyloidosis, with a median hematological response observed after 1 month [31]. In all cases, daratumumab was associated with a very tolerable AEs profile.

ANDROMEDA was a landmark phase III clinical trial where subcutaneous daratumumab was investigated in combination with CyBorD versus a regimen of CyBorD alone in 388 patients newly diagnosed with AL amyloidosis with equal to or more than one organ involved and with an Eastern Cooperative Oncology Group (ECOG) performance scale of 0 - 2 [32, 33]. The overall hematological response was significantly higher in the daratumumab + CyBorD group (92% including a CR of 53%), compared to the CyBorD group (77% including a CR in 18%). There was also a significant improvement in 6-month organ response, with 42% achieving cardiac response (versus 22%) and 54% achieving renal response (versus 27%).

Along with the deeper and more rapid hematological response in AL amyloidosis, daratumumab is also attractive given its potential for subcutaneous dosing, saving patients with cardiac involvement from receiving a higher amount of fluid. There was a small risk increase in grade 3-4 toxicity in the daratumumab combination group, particularly lymphopenia (13% with the daratumumab combination vs. 10% with CyBorD alone) and pneumonia (8% vs. 4%, respectively). However, the reported discontinuation rate because of adverse treatment events was only 4% in the daratumumab cohort.

Targeting Amyloid Component Therapy

In AL amyloidosis, the burden of symptoms often depends on the burden of amyloid deposition into organs; hence, researchers must not only develop drugs that slow or kill the malignant PCs but also target the products of the misfolded light chain. NEOD001, a monoclonal antibody that targets a specific epitope that is present only on abnormally folded light chains, can bind and neutralize them by facilitating absorption and clearance [103]. NEOD001 was initially evaluated in a phase I/II clinical trial with encouraging results [105]; however, subsequent studies failed to prove a significant improvement in outcomes [34, 104]. Subgroup analysis of VITAL suggested benefit in Mayo Stage IV patients with severe cardiac involvement and a confirmatory trial with this medication (now called birtamimab) is planned in this population [34].

CAEL-101 is another monoclonal antibody that has a strong affinity to kappa and lambda light chains and is a by-product of monoclonal PC malignant expansion. When it binds to kappa and lambda light chains, it initiates neutrophil-mediated phagocytosis, enhancing the clearance of these light chains. This may decrease the light chain burden on organs and improve overall organ response to AL amyloidosis treatment [35, 36]. An initial analysis of a phase I a/b clinical trial showed an objective cardiac and renal response in 67% of the patients with no reported grade 4/5 AEs [105].

Bendamustine Therapy

Bendamustine is a chemotherapeutic agent that has properties of both alkylators and antimetabolite and was approved by the FDA in 2008 for chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) [106, 107]. A retrospective study of 122 patients with refractory/relapsed AL amyloidosis treated with bendamustine and prednisolone showed a better hematological response in patients with IgM-AL amyloidosis compared to patients with non-IgM-AL amyloidosis (58% vs. 28%, respectively); however, the overall hematological response was 35% only with a median PFS of 9 months [37]. Another multicenter phase II trial investigated the role of bendamustine and dexamethasone (Ben-D) in a total of 31 patients with progressive or persistent AL amyloidosis after receiving at least one therapy or more [108]. The Ben-D combination achieved a PR of 57% or better, and median PFS and median OS of 11.3 and 18.2 months, respectively. Two-thirds of patients developed grade 3-4 toxicities, with myelosuppression and fatigue being the most common. As noted above, the effect of bendamustine in refractory/relapsed AL amyloidosis is unclear and more research is needed in order to investigate its role.

Small Molecules

Doxycycline

Doxycycline is an antimicrobial drug that interferes with protein synthesis by binding to certain sites on the ribosomes; perhaps doxycycline decreases the burden of misfolded protein aggregation in amyloidosis through this mechanism [109, 110]. An observational study showed that doxycycline improves the median OS when used as a prophylactic antimicrobial agent for patients who underwent ASCT compared to other patients who received penicillin, and particularly in patients who achieved hematological response [111]. A similar outcome was reported by Wechalekar et al, who compared doxycycline administration along with standard chemotherapeutics for cardiac AL amyloidosis in 30 patients to 73 matched historical controls; the therapy was associated with

a better overall hematological response compared to a control group (93% vs. 59%, respectively), as well as better 12- and 24-month survival rates (82% vs. 53% and 82% vs. 40%, respectively) [38]. A recently published prospective phase II trial was able to prove that long-term treatment with doxycycline in patients with newly diagnosed AL amyloidosis was not only associated with a decrease in mortality and a safe profile but also with increased transplant utilization after receiving triple induction chemotherapy with a post-ASCT 100-day mortality rate of 0 [112].

Venteoclax

Venteoclax is a small molecule that has a biological inhibitory effect on the mutated gene t(11;14), which is found in B-cell lymphoma, MM, and in up to 50% of AL amyloidosis patients [74]. Venteoclax was able to achieve a CR in a 67-year-old man with refractory systemic AL amyloidosis harboring t(11;14) after failing a CyBorD regimen [113]. Though a phase III study that was designed to investigate the role of venteoclax in combination with BD in relapsed/refractory MM was suspended due to an increased risk of death in the venteoclax cohort (NCT02755597), the data from a case series using venteoclax in refractory/relapsed AL amyloidosis showed significant results in term of achieving CR without experiencing serious AEs [114, 115]. This is especially important, as bortezomib is often less responsive in patients with this t(11;14) mutation. Venteoclax use remains a notion that could bring hope for refractory/relapsed AL amyloidosis patients, which indeed necessitates more studies to be conducted on safety and efficacy.

Epigallocatechin-3-gallate (ECGC)

Cardiac involvement in AL amyloidosis is considered to be one of the major factors that determine disease severity, choice of initial therapy, and the expected outcome of the treatment. ECGC is a major antioxidant that is found naturally in green tea and has been proven to exert some effects on misfolded amyloid fibrils, rendering them into a more benign form that does not polymerize into insoluble fibrils and does not exert a cytotoxic effect when aggregated in the extracellular matrix [39]. ECGC was introduced as adjuvant therapy in the management of AL amyloidosis, particularly in cardiac AL amyloidosis, based on a favorable result reported in a case reports after a hematologist, Werner Hunstein, treated himself with high doses of this agent [39, 40]. In TAME-AL, a completed phase II randomized clinical trial that was designed to investigate the effect of a 12-month course of ECGC on the left ventricular mass in cardiac AL amyloidosis, the final results have not yet been published (NCT02015312).

Conclusions

AL amyloidosis is a systemic disease with a high mortality rate. ASCT has been the preferred treatment in eligible patients; however, randomized clinical trials showing benefit over conventional treatment are lacking. Steroids, alkylating agents, and PIs have emerged as the first-line combination drug therapy in patients with AL amyloidosis, with the most common regimen being CyBorD. Recently, daratumumab has demonstrated improved outcomes when combined with CyBorD with a low side effect profile and should be considered as first-line therapy. IMiDs are less favorable as first-line therapy for AL amyloidosis but should be considered strongly in cases of refractory/relapsed disease or for maintenance therapy. Since treatment of AL amyloidosis is based mainly on experiences in MM, researches focused on a better understanding of AL amyloidosis pathology as well as targeted clinical trials are essential.

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Conflict of Interest

The authors declare they do not have a conflict of interest.

Author Contributions

ME, NA, BS, and SR involved in the design of the study, literature review, data interpretation, and manuscript writing. SU, HH, JI, AS, MB, and LS involved in critical review of literature, independent data, and manuscript writing.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Abbreviations

MM: multiple myeloma; OS: overall survival; CR: complete response; VGPR: very good partial response; PR: partial response

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