Conventional Therapy for Amyloid Light-Chain Amyloidosis

Paolo Milani Giovanni Palladini

Amyloidosis Research and Treatment Center, Foundation IRCCS Policlinico San Matteo, and Department of Molecular Medicine, University of Pavia, Pavia, Italy

Keywords

Amyloidosis · Cancer therapy · Clinical studies

Abstract

The vast majority of patients with light-chain (AL) amyloidosis are not eligible for stem cell transplant and are treated with conventional chemotherapy. Conventional regimens are based on various combinations of dexamethasone, alkylating agents, proteasome inhibitors, and immunomodulatory drugs. The choice of these regimens requires a careful risk stratification, based on the extent of amyloid organ involvement, comorbidities, and the characteristics of the amyloidogenic plasma cell clone. Most patients are treated upfront with bortezomib and dexamethasone combined with cyclophosphamide or melphalan. Cyclophosphamide does not compromise stem cell mobilization and harvest and is more manageable in renal failure. Melphalan can overcome the effect of t(11;14), which is associated with lower response rates and shorter survival in subjects treated with bortezomib and dexamethasone, or in combination with cyclophosphamide. Lenalidomide and pomalidomide are the mainstay of rescue treatment. They are effective in patients exposed to bortezomib, dexamethasone, and alkylators, but deep hematologic responses are rare. Ixazomib, alone or in

combination with lenalidomide, increases the rate of complete responses in relapsed/refractory patients. Conventional chemotherapy regimens will represent the backbone for future combinations, particularly with anti-plasma-cell immunotherapy, that will further improve response rates and outcomes.

© 2020 S. Karger AG, Basel

Introduction

In amyloid light-chain (AL) amyloidosis, the choice of treatment is largely dependent on the extent and severity of amyloid organ involvement [1]. Only a minority of subjects, ranging from 15 to 25% according to differences in eligibility criteria and the composition of the patient population, can be offered autologous stem cell transplantation (ASCT). Thus, conventional, nontransplant therapy is of utmost importance in the treatment of this disease. For many years, only a few, scarcely effective options have been available. Nevertheless, 2 randomized trials, of melphalan and prednisone with or without colchicine versus colchicine alone, made clear that the administration of plasma-cell chemotherapy improves the survival of patients with AL amyloidosis [2, 3]. Until re-

cently, these 2 studies were the only prospective clinical trials showing an overall survival (OS) advantage in this disease. Subsequently, progress made in multiple myeloma studies has gradually enriched the therapeutic armamentarium. Currently, dexamethasone, alkylating agents, proteasome inhibitors, and immunomodulatory drugs (IMiDs) in various combinations, are used to treat patients with AL amyloidosis. However, there are very few controlled studies investigating the most appropriate treatment for different settings, and the design of the treatment strategy relies on expert opinions mostly based on retrospective trials. Moreover, patients with AL amyloidosis who are not eligible for ASCT are not a homogeneous population. They may be transplant candidates if they adequately respond to upfront treatment, or very fragile patients who are at a high risk of death in the first weeks after diagnosis. An accurate risk assessment should therefore be the first step in the design of the treatment strategy.

Risk Assessment

Several factors need to be considered in the selection of the most appropriate regimen for patients with AL amyloidosis who are not eligible for ASCT (Table 1). The severity of heart involvement is the most important determinant of survival in AL amyloidosis. This is best assessed by measuring the cardiac biomarkers N-terminal pro-natriuretic peptide type B (NT-proBNP) and cardiac troponins (cTn). While patients without heart involvement or who have only mild-to-moderate cardiac dysfunction can be considered for ASCT, subjects with advanced heart involvement require precautions also when administering conventional chemotherapy. Cardiac stage IIb subjects, identified by elevated troponins (i.e., cTnI >0.1 ng/mL, cTnT >0.035 µg/L, or high-sensitivity cTnT >54 ng/L) and very high NT-proBNP (>8500 ng/L) or BNP (>700 ng/L) have a median survival of a few months [4–6]. These subjects, as well as those with clinically severe (New York Heart Association [NYHA] class III or IV) heart failure should receive treatment, particularly steroids, at a reduced dosage or under intensive care support [1]. However, only a rapid and profound reduction of the amyloid light chains can improve survival in these severely ill patients [7], and dose reduction may decrease the likelihood of reaching this goal. Repetitive ventricular arrhythmia has been reported to predict sudden death in patients with cardiac AL amyloidosis treated with high-dose dexamethasone [8, 9], and a steroid dose reduction

is advisable also in patients with this risk factor. Treatment with thalidomide was reported to be associated with symptomatic bradyarrhythmia in patients with AL amyloidosis [10], and periodic monitoring is recommended in patients receiving this drug.

Specific comorbidities and disease-related clinical manifestations should also be considered when designing the treatment strategy in patients with AL amyloidosis [1]. Approximately 15% of patients present with clinically significant peripheral neuropathy. Potentially neurotoxic drugs, such as bortezomib and thalidomide, should be avoided or used with exceeding caution and under close monitoring in these patients. In patients with neuropathy, proteasome inhibition with carfilzomib can be considered, carefully balancing the potential cardiac toxicity of this drug [11]. The coexistence of fibrotic lung disease can also discourage the use of bortezomib [12, 13]. Furthermore, cyclophosphamide is preferable to melphalan in subjects with renal failure. In such patients, a melphalan dose reduction is required [14, 15]. Finally, lenalidomide was reported to be associated with worsening renal function in patients with proteinuria [16], which is present in approximately two-thirds of subjects with AL amyloidosis.

Some characteristics of the amyloid clone have recently emerged as additional factors to be considered in the choice of therapy. The presence of the chromosomal abnormality t(11;14), found in approximately 50% of patients with AL amyloidosis, is associated with lower response rates and shorter survival in patients treated with bortezomib/dexamethasone alone or in combination with cyclophosphamide [17, 18]. Melphalan can overcome this unfavorable effect and could be considered for these patients; on the other hand, gain 1(q21) predicts a poorer outcome with oral melphalan, and subjects carrying this abnormality should be offered bortezomib when possible [19].

Finally, it should be considered that some contraindications that preclude ASCT upfront can be reversible if patients respond to front-line conventional therapy [20]. In these subjects, stem cell-sparing treatments should be employed, in order to preserve the possibility of performing second-line ASCT.

Upfront Conventional Treatment

After early reports of activity of melphalan/prednisone [2, 3] and high-dose dexamethasone [21] in AL amyloidosis, the oral combination of melphalan and dexameth-

Table 1. Risk assessment factors for conventional therapy

Factor	Clinical/laboratory assessment	Precautions
Advanced heart involvement	Stage IIIb patients NYHA class III and IV	Reduce steroid dosage ICU support
Repetitive ventricular arrhythmia (RVA)	ECG Holter monitoring	Reduce steroid dosage
Bradyarrhythmia	ECG Holter monitoring	Avoid thalidomide (or use it with caution) When thalidomide is administered, periodic Holter monitoring is recommended
Clinically significant peripheral neuropathy	Clinical evaluation EMG/ENG monitoring	Avoid/use with caution potentially neurotoxic agents such as bortezomib or thalidomide
Fibrotic lung disease	Chest X-ray HR-CT evaluation	Avoid bortezomib (or use it with caution)
Nephrotic-range proteinuria and a reduced glomerular filtration rate	eGFR 24-h proteinuria	Avoid lenalidomide (or use it with caution)
t(11;14)	iFISH on BMPC	Response rates and survival are reduced with bortezomib/dexamethasone and cyclophosphamide. Consider using oral melphalan in combination with dexamethasone and/or bortezomib
Gain 1(q21)	iFISH on BMPC	Response rates and survival with melphalan/dexamethasone are reduced. Consider bortezomib
Potentially reversible contraindications to ASCT	Consider patient's age and the degree of organ involvement	Avoid oral melphalan

Cardiac staging (European staging) according to Wechalekar et al. [4] is based on levels of troponins and NT-proBNP: thresholds for cTnI (or hs-cTnI) and NT-proBNP are <0.1 ng/mL (<77 ng/L), and <332 ng/L, respectively. Stage III cardiac involvement is defined as cTnI >0.1 ng/mL (or hs-cTnI >77 ng/L) and NT-proBNP >332 ng/L (provided the NT-proBNP is <8,500 ng/L). Stage II patients have 1 value of either troponin or NT-proBNP above the thresholds. Stage I patients have troponin and NT-proBNP below the thresholds. Stage IIIb are patients in stage III with NT-proBNP ≥8,500 ng/L.

Cardiac staging according to Lillenes et al. [6] is based on thresholds for cTnI and BNP of <0.1 ng/mL and <81 pg/mL, respectively. Stage III cardiac involvement is defined as a cTnI >0.1 ng/mL and BNP >81 ng/L (provided the BNP is <700 pg/mL). Stage II patients have 1 value of either troponin or BNP above the thresholds. Stage I patients have troponin and BNP below the thresholds. Stage IIIb are patients in stage III with BNP ≥700 pg/mL.

EMG, electromyography; ENG, electroneurography; HR-CT, high-resolution computer tomography; eGFR, estimated glomerular filtration rate; t(11;14), translocation (11;14); iFISH, interphase fluorescence in situ hybridization; BMPC, bone marrow plasma-cell infiltrate; ASCT, autologous stem cell transplant.

asone (MDex) was proposed as an upfront treatment [22]. The tolerability of this regimen is excellent, and hematologic response rates range from 50 to 75%, with a complete response (CR) in 20–30% of patients depending on the disease stage and the possibility of administering full-dose dexamethasone [23]. Before biomarker-based eligibility criteria were adopted to select transplant candidates, a French multicenter randomized trial compared MDex and ASCT [24]. The study showed no difference in response rates and survival in a landmark analysis excluding early transplant-related mortality. A median survival

exceeding 7 years was reported for intermediate-risk patients treated with MDex up front [23]. Thus, MDex has long been considered a standard treatment for patients with AL amyloidosis. The landscape changed when the proteasome inhibitor bortezomib became available. Proteasome inhibition is an appealing therapeutic strategy for AL amyloidosis, because the amyloidogenic plasma cells rely on the proteasome to cope with the proteotoxicity imposed by the light chain they produce [25]. Early studies reported an overall hematologic response rate as high as 90% with CR in 60% of patients with a treatment

combination of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) [26, 27]. Early enthusiasm was tempered by larger, real-world studies showing a hematologic response in 60–65% of patients (CR 21–25%) and a median survival of 6 years [5, 28]. In the patients treated with CyBorD, cardiac stage is the main determinant of survival [5, 28]. Bortezomib and dexamethasone can also be combined with melphalan (BMDex) [29]. This was compared with MDex in a randomized trial that showed a higher overall hematologic response rate of 81% (vs. 57%) and prolonged survival in the BMDex arm [30]. Unfortunately, no controlled study has yet established the best bortezomib-based combination. Cyclophosphamide is manageable in patients with renal failure and does not compromise the subsequent mobilization and harvest of stem cells. Melphalan is more effective in patients harboring t(11;14) and, combined with bortezomib, it is associated with a longer response [31]. Of note, a retrospective study showed that the addition of cyclophosphamide and a combination with higher doses of dexamethasone do not significantly improve the response rate or survival of patients treated with bortezomib [32].

Immunomodulatory drugs can be combined with dexamethasone and alkylators upfront. The combination of cyclophosphamide, thalidomide, and dexamethasone (CTD) grants a hematologic response in 74–79% of patients (CR 21–25%) [33, 34]. The combination of cyclophosphamide, lenalidomide, and dexamethasone was also used upfront, and obtained a hematologic response in 46–54% of patients and CR in 25% [35, 36]. Hegenbart et al. [37] reported a 68% hematologic response rate (CR 18%) with lenalidomide combined with MDex. Lenalidomide can also be combined with bortezomib and dexamethasone. This regimen grants a remarkably high hematologic response rate (89%; CR 32%) and, importantly, the response is fast, being achieved after a single cycle in most cases [38].

Conventional Treatment of Relapsed and Refractory Patients

If relapse occurs after a relevant time (a minimum of 6 months) after the discontinuation of upfront therapy, rechallenge with the agents used up front can be considered. However, this is associated with a shorter progression-free survival compared to switching to other drugs, although overall survival is not affected [39].

Immunomodulatory drugs are commonly used in the relapsed/refractory setting. Lenalidomide alone or in

combination with dexamethasone has been studied in prospective phase II trials and retrospective series [40–43]. The overall hematologic response rate ranged from 38 to 61%. Triple combinations including lenalidomide, dexamethasone, and cyclophosphamide have also been tested, and there was a hematologic response in approximately 60% of patients [36, 44, 45]. With lenalidomide, the quality of the response is generally low, with CR observed in <10% of cases. Nevertheless, prolonged treatment may improve the CR rate (to 20%) and grants a noteworthy renal response rate (of 55%) [43]. Importantly, lenalidomide is effective in subjects exposed to ASCT, oral alkylating agents, bortezomib, and thalidomide [36, 42, 43, 45]. Of note, the maximum tolerated daily dose of lenalidomide for AL amyloidosis patients is 15 mg, which is lower than that commonly used in multiple myeloma. Based on the encouraging results with lenalidomide, pomalidomide only (or in combination with dexamethasone) was also used to rescue patients with AL amyloidosis [46–49]. In these studies, the overall hematologic response rate ranged from 44 to 68%, with CR in 0–30% of cases. The response to pomalidomide is fast, being achieved after 1 cycle in most cases, and, similarly to lenalidomide, pomalidomide is effective in patients exposed to alkylating agents, bortezomib, and earlier-generation IMiDs [48].

Two European studies [50, 51] showed that bendamustine can be used as a rescue agent in patients with AL amyloidosis. The overall hematologic response rate to this drug is 35% and a CR is rare. However, bendamustine, particularly in combination with rituximab, seems more effective in patients who have an underlying IgM-producing clone. In these subjects, a hematologic response is obtained in almost 60% of cases and a CR in approximately 10% [50, 51].

Recently, the second-generation orally active proteasome inhibitor, ixazomib, was reported to be active in relapsed/refractory AL amyloidosis. In a small phase II trial, the overall hematologic response rate was 52% and 10% of subjects reached CR [52]. Remarkably, all 5 patients who had not been previously exposed to bortezomib responded to ixazomib, and 2 of them achieved CR [52]. The results of a randomized phase III clinical trial of ixazomib versus physician's best choice was recently presented at a meeting of the American Society of Hematology [53]. The comparator arm was lenalidomide plus dexamethasone in 57% of cases. In this trial, in both arms, only 47% of patients had received prior bortezomib which makes the study population only partly representative of real-world relapsed/refractory AL amyloidosis. The primary end point was overall hematologic response rate, which was 53% in the ixazo-

Table 2. Ongoing clinical trials in AL amyloidosis (adapted from Clinicaltrials.gov)

Phase	Trial ID	Regimen
Newly diagnosed patients		
I/II	NCT03236792	ixazomib, cyclophosphamide, and dexamethasone
I/II	NCT01864018	ixazomib, cyclophosphamide, and dexamethasone
III	NCT03201965	daratumumab with cyclophosphamide, bortezomib, and dexamethasone (CyBorD) vs. CyBorD alone.
II/III	NCT03474458	doxycycline vs. standard of care plus bortezomib-based therapy.
II	NCT03401372	CyBorD with or without doxycycline in Mayo stage II/III amyloidosis
II	NCT04131309	daratumumab in stage III untreated patients
Relapsed/refractory patients		
III	NCT01659658	ixazomib plus dexamethasone vs. physician's best choice
II	NCT03618537	ixazomib maintenance study on patients with AL amyloidosis
II	NCT03499808	isatuximab in AL amyloidosis
II	NCT03252600	Lenalidomide, dexamethasone, and elotuzumab with or without cyclophosphamide
II	NCT03283917	daratumumab, ixazomib, and dexamethasone (also for newly diagnosed patients)
II	NCT04115956	melphalan in AL amyloidosis
II	NCT03315026	siltuximab after ASCT in multiple myeloma and AL amyloidosis

mib arm and 51% in the comparator arm. Nevertheless, CR was more frequent with ixazomib (26 vs. 18%), and treatment with ixazomib was associated with a significantly longer progression-free survival. Furthermore, the patients who received ixazomib had a higher rate of cardiac and renal responses. More recently, investigators from the UK National Amyloidosis Centre reported their retrospective experience with a combination of ixazomib, lenalidomide, and dexamethasone [54]. Overall, they observed a 64% hematological response rate with CR in 26% of patients, reached within 2 months in almost all cases. In this study, all patients had been previously exposed to bortezomib, and 30% had received prior lenalidomide. No CR was seen in the subjects who had been previously treated with lenalidomide or bortezomib. These recent data indicate that rescue treatment with ixazomib grants a more profound hematologic response than the available alternatives. This drug, alone or in combination with lenalidomide, is thus an appealing option, particularly for subjects who are not refractory to bortezomib.

Since the amyloid plasma-cell clone harbors the t(11;14) chromosomal abnormality in approximately 50% of cases, the Bcl-2 inhibitor venetoclax is being considered as a potentially effective agent in a substantial proportion of patients with AL amyloidosis. No systematic study has been reported so far; however, several case reports suggest that venetoclax can effectively rescue heavily pre-treated patients with this disease [55–57].

Conclusion

Currently, bortezomib combined with dexamethasone and alkylators can be considered the standard conventional treatment for AL amyloidosis. These agents represent the backbone of future, more powerful combinations. In the near future, anti-plasma-cell immunotherapy, particularly daratumumab, will likely be added to these combinations in the search for a novel standard of care. It is possible that combinations of potent IMiDs and daratumumab and/or ixazomib will soon improve the treatment of relapsed/refractory patients [58–61].

Future studies will further advance our knowledge and ability to treat patients with AL amyloidosis. An ever-increasing number of clinical trials is being designed (Table 2) and newer agents are already being tested. Ongoing and future studies will elucidate the role of immunotherapy (daratumumab, elotuzumab, siltuximab, and isatuximab). The role of novel powerful alkylators, such as melflufen (NCT04115956), will be explored. Interfering with amyloidogenesis and organ damage is an interesting area for future research. For instance, our group showed that a small molecule, anthracycline 4'-iodo-4'-deoxy-doxorubicin (I-DOX), inhibits amyloidogenesis in vitro, and could improve the clinical status and promote resorption of amyloid deposits in patients with AL amyloidosis [62, 63]. A compound whose molecular structure closely resembles that of I-DOX, i.e., the anti-

biotic doxycycline, was also shown to disrupt amyloid fibrils in vitro and reduce the amyloid load in a transgenic mouse model [64], and to counteract the proteotoxicity of amyloidogenic light chains in a *Caenorhabditis elegans* model [65]. A retrospective case-control study showed that the addition of doxycycline to conventional chemotherapy improved the survival of patients with cardiac AL amyloidosis. Two randomized phase III studies of doxycycline plus bortezomib-based chemotherapy versus chemotherapy alone are ongoing (NCT03474458 and NCT03401372).

Despite the paucity of controlled studies and the rarity of AL amyloidosis, major advancements have been made in the conventional treatment of patients with this disease, thanks to the perseverance of the still small, but growing, community of physicians and scientists working on AL amyloidosis, the foresight of pharmaceutical companies getting involved in research into this rare disease, and, most importantly, the courage of the patients

suffering from AL amyloidosis and their families. The advancements made in the field of conventional treatment offer a solid background for future developments.

Disclosure Statement

P.M.: speaker honoraria from Pfizer and Janssen-Cilag, and travel support from Celgene; G.P.: honoraria from and on the advisory board of Janssen-Cilag, and travel grants from Celgene.

Funding Sources

P.M. is partially supported by a fellowship award from Collegio Ghislieri, Pavia.

Author Contributions

P.M. and G.P. both wrote the manuscript.

References

- Merlini G, Dispenzieri A, Santhorawala V, Schönland SO, Palladini G, Hawkins PN, et al. Systemic immunoglobulin light chain amyloidosis. *Nat Rev Dis Primers*. 2018 Oct;4(1):38.
- Skinner M, Anderson J, Simms R, Falk R, Wang M, Libbey C, et al. Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. *Am J Med*. 1996 Mar;100(3):290–8.
- Kyle RA, Gertz MA, Greipp PR, Witzig TE, Lust JA, Lacy MQ, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med*. 1997 Apr;336(17):1202–7.
- Wechalekar AD, Schönland SO, Kastritis E, Gillmore JD, Dimopoulos MA, Lane T, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. *Blood*. 2013 Apr;121(17):3420–7.
- Palladini G, Sachchithanatham S, Milani P, Gillmore J, Folini A, Lachmann H, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. *Blood*. 2015 Jul;126(5):612–5.
- Lillness B, Ruberg FL, Mussinelli R, Doros G, Santhorawala V. Development and validation of a survival staging system incorporating BNP in patients with light chain amyloidosis. *Blood*. 2019 Jan;133(3):215–23.
- Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. *N Engl J Med*. 2018 Jul;379(1):22–31.
- Palladini G, Malamani G, Cò F, Pistorio A, Recusani F, Anesi E, et al. Holter monitoring in AL amyloidosis: prognostic implications. *Pacing Clin Electrophysiol*. 2001 Aug;24(8 Pt 1):1228–33.
- Palladini G, Anesi E, Perfetti V, Obici L, Invernizzi R, Balduini C, et al. A modified high-dose dexamethasone regimen for primary systemic (AL) amyloidosis. *Br J Haematol*. 2001 Jun;113(4):1044–6.
- Palladini G, Perfetti V, Perlini S, Obici L, Lavatelli F, Caccialanza R, et al. The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). *Blood*. 2005 Apr;105(7):2949–51.
- Manwani R, Mahmood S, Sachchithanatham S, Lachmann HJ, Gillmore JD, Yong K, et al. Carfilzomib is an effective upfront treatment in AL amyloidosis patients with peripheral and autonomic neuropathy. *Br J Haematol*. 2019 Dec;187(5):638–41.
- Zappasodi P, Dore R, Castagnola C, Astori C, Varettoni M, Mangiacavalli S, et al. Rapid response to high-dose steroids of severe bortezomib-related pulmonary complication in multiple myeloma. *J Clin Oncol*. 2007 Aug;25(22):3380–1.
- Miyakoshi S, Kami M, Yuji K, Matsumura T, Takatoku M, Sasaki M, et al. Severe pulmonary complications in Japanese patients after bortezomib treatment for refractory multiple myeloma. *Blood*. 2006 May;107(9):3492–4.
- Dimopoulos MA, Sonneveld P, Leung N, Merlini G, Ludwig H, Kastritis E, et al. International Myeloma Working Group Recommendations for the Diagnosis and Management of Myeloma-Related Renal Impairment. *J Clin Oncol*. 2016 May;34(13):1544–57.
- Carlson K, Hjorth M, Knudsen LM; Nordic Myeloma Study Group. Toxicity in standard melphalan-prednisone therapy among myeloma patients with renal failure—a retrospective analysis and recommendations for dose adjustment. *Br J Haematol*. 2005 Mar;128(5):631–5.
- Specter R, Santhorawala V, Seldin DC, Shelton A, Fennessey S, Finn KT, et al. Kidney dysfunction during lenalidomide treatment for AL amyloidosis. *Nephrol Dial Transplant*. 2011 Mar;26(3):881–6.
- Bochtler T, Hegenbart U, Kunz C, Granzow M, Benner A, Seckinger A, et al. Translocation t(11;14) is associated with adverse outcome in patients with newly diagnosed AL amyloidosis when treated with bortezomib-based regimens. *J Clin Oncol*. 2015 Apr;33(12):1371–8.
- Muchtar E, Dispenzieri A, Kumar SK, Ketterling RP, Dingli D, Lacy MQ, et al. Interphase fluorescence in situ hybridization in untreated AL amyloidosis has an independent prognostic impact by abnormality type and treatment category. *Leukemia*. 2017 Jul;31(7):1562–9.
- Bochtler T, Hegenbart U, Kunz C, Benner A, Seckinger A, Dietrich S, et al. Gain of chromosome 1q21 is an independent adverse prognostic factor in light chain amyloidosis patients treated with melphalan/dexamethasone. *Amyloid*. 2014 Mar;21(1):9–17.

- 20 Manwani R, Hegenbart U, Mahmood S, Sachchithanantham S, Kyriakou C, Yong K, et al. Deferred autologous stem cell transplantation in systemic AL amyloidosis. *Blood Cancer J*. 2018 Nov;8(11):101.
- 21 Dhodapkar MV, Hussein MA, Rasmussen E, Solomon A, Larson RA, Crowley JJ, et al.; United States Intergroup Trial Southwest Oncology Group. Clinical efficacy of high-dose dexamethasone with maintenance dexamethasone/alpha interferon in patients with primary systemic amyloidosis: results of United States Intergroup Trial Southwest Oncology Group (SWOG) S9628. *Blood*. 2004 Dec;104(12):3520–6.
- 22 Palladini G, Perfetti V, Obici L, Caccialanza R, Semino A, Adami F, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. *Blood*. 2004 Apr;103(8):2936–8.
- 23 Palladini G, Milani P, Foli A, Obici L, Lavatelli F, Nuvolone M, et al. Oral melphalan and dexamethasone grants extended survival with minimal toxicity in AL amyloidosis: long-term results of a risk-adapted approach. *Haematologica*. 2014 Apr;99(4):743–50.
- 24 Jaccard A, Moreau P, Leblond V, Leleu X, Benboubker L, Hermine O, et al.; Myélome Autogreffe (MAG) and Intergroupe Franco-phone du Myélome (IFM) Intergroup. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med*. 2007 Sep;357(11):1083–93.
- 25 Oliva L, Orfanelli U, Resnati M, Raimondi A, Orsi A, Milan E, et al. The amyloidogenic light chain is a stressor that sensitizes plasma cells to proteasome inhibitor toxicity. *Blood*. 2017 Apr;129(15):2132–42.
- 26 Venner CP, Lane T, Foard D, Rannigan L, Gibbs SD, Pinney JH, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. *Blood*. 2012 May;119(19):4387–90.
- 27 Mikhael JR, Schuster SR, Jimenez-Zepeda VH, Bello N, Spong J, Reeder CB, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. *Blood*. 2012 May;119(19):4391–4.
- 28 Manwani R, Cohen O, Sharpley F, Mahmood S, Sachchithanantham S, Foard D, et al. A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib. *Blood*. 2019 Dec;134(25):2271–80.
- 29 Palladini G, Milani P, Foli A, Vidus Rosin M, Basset M, Lavatelli F, et al. Melphalan and dexamethasone with or without bortezomib in newly diagnosed AL amyloidosis: a matched case-control study on 174 patients. *Leukemia*. 2014 Dec;28(12):2311–6.
- 30 Kastritis E, Leleu X, Bertrand A, Zamagni E, Mollee P, Cibeira MT, et al. A Randomized Phase III Trial of Melphalan and Dexamethasone (MDex) versus Bortezomib, Melphalan and Dexamethasone (BMDex) for Untreated Patients with AL Amyloidosis. *Blood*. 2014;124(21):1.
- 31 Palladini G, Milani P, Foli A, Basset M, Russo F, Perlino S, et al. Presentation and outcome with second-line treatment in AL amyloidosis previously sensitive to nontransplant therapies. *Blood*. 2018 Feb;131(5):525–32.
- 32 Kastritis E, Gavriatopoulou M, Roussou M, Fotiou D, Ziogas DC, Migkou M, et al. Addition of cyclophosphamide and higher doses of dexamethasone do not improve outcomes of patients with AL amyloidosis treated with bortezomib. *Blood Cancer J*. 2017 Jun;7(6):e570.
- 33 Wechalekar AD, Goodman HJ, Lachmann HJ, Offer M, Hawkins PN, Gillmore JD. Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. *Blood*. 2007 Jan;109(2):457–64.
- 34 Venner CP, Gillmore JD, Sachchithanantham S, Mahmood S, Lane T, Foard D, et al. A matched comparison of cyclophosphamide, bortezomib and dexamethasone (CVD) versus risk-adapted cyclophosphamide, thalidomide and dexamethasone (CTD) in AL amyloidosis. *Leukemia*. 2014 Dec;28(12):2304–10.
- 35 Cibeira MT, Oriol A, Lahuerta JJ, Mateos MV, de la Rubia J, Hernández MT, et al.; PETHEMA cooperative study group. A phase II trial of lenalidomide, dexamethasone and cyclophosphamide for newly diagnosed patients with systemic immunoglobulin light chain amyloidosis. *Br J Haematol*. 2015 Sep;170(6):804–13.
- 36 Kastritis E, Terpos E, Roussou M, Gavriatopoulou M, Pamboukas C, Boletis I, et al. A phase 1/2 study of lenalidomide with low-dose oral cyclophosphamide and low-dose dexamethasone (RdC) in AL amyloidosis. *Blood*. 2012 Jun;119(23):5384–90.
- 37 Hegenbart U, Bochtler T, Benner A, Becker N, Kimmich C, Kristen AV, et al. Lenalidomide/melphalan/dexamethasone in newly diagnosed patients with immunoglobulin light chain amyloidosis: results of a prospective phase 2 study with long-term follow up. *Haematologica*. 2017 Aug;102(8):1424–31.
- 38 Kastritis E, Dialoupi I, Gavriatopoulou M, Roussou M, Kanellias N, Fotiou D, et al. Primary treatment of light-chain amyloidosis with bortezomib, lenalidomide, and dexamethasone. *Blood Adv*. 2019 Oct;3(20):3002–9.
- 39 Tandon N, Sidana S, Gertz MA, Dispenzieri A, Lacy MQ, Buadi FK, et al. Treatment patterns and outcome following initial relapse or refractory disease in patients with systemic light chain amyloidosis. *Am J Hematol*. 2017 Jun;92(6):549–54.
- 40 Dispenzieri A, Lacy MQ, Zeldenrust SR, Hayman SR, Kumar SK, Geyer SM, et al. The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. *Blood*. 2007 Jan;109(2):465–70.
- 41 Sanchirawala V, Wright DG, Rosenzweig M, Finn KT, Fennessey S, Zeldis JB, et al. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. *Blood*. 2007 Jan;109(2):492–6.
- 42 Palladini G, Russo P, Foli A, Milani P, Lavatelli F, Obici L, et al. Salvage therapy with lenalidomide and dexamethasone in patients with advanced AL amyloidosis refractory to melphalan, bortezomib, and thalidomide. *Ann Hematol*. 2012 Jan;91(1):89–92.
- 43 Mahmood S, Venner CP, Sachchithanantham S, Lane T, Rannigan L, Foard D, et al. Lenalidomide and dexamethasone for systemic AL amyloidosis following prior treatment with thalidomide or bortezomib regimens. *Br J Haematol*. 2014 Sep;166(6):842–8.
- 44 Kumar SK, Hayman SR, Buadi FK, Roy V, Lacy MQ, Gertz MA, et al. Lenalidomide, cyclophosphamide, and dexamethasone (CRd) for light-chain amyloidosis: long-term results from a phase 2 trial. *Blood*. 2012 May;119(21):4860–7.
- 45 Palladini G, Russo P, Milani P, Foli A, Lavatelli F, Nuvolone M, et al. A phase II trial of cyclophosphamide, lenalidomide and dexamethasone in previously treated patients with AL amyloidosis. *Haematologica*. 2013 Mar;98(3):433–6.
- 46 Dispenzieri A, Buadi F, Laumann K, LaPlant B, Hayman SR, Kumar SK, et al. Activity of pomalidomide in patients with immunoglobulin light-chain amyloidosis. *Blood*. 2012 Jun;119(23):5397–404.
- 47 Sanchirawala V, Shelton AC, Lo S, Varga C, Sloan JM, Seldin DC. Pomalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 1 and 2 trial. *Blood*. 2016 Aug;128(8):1059–62.
- 48 Palladini G, Milani P, Foli A, Basset M, Russo F, Perlino S, et al. A phase 2 trial of pomalidomide and dexamethasone rescue treatment in patients with AL amyloidosis. *Blood*. 2017 Apr;129(15):2120–3.
- 49 Sharpley FA, Manwani R, Mahmood S, Sachchithanantham S, Lachmann H, Gilmore J, et al. Real-world outcomes of pomalidomide for treatment of relapsed light chain amyloidosis. *Br J Haematol*. 2018 Nov;183(4):557–63.
- 50 Manwani R, Sachchithanantham S, Mahmood S, Foard D, Sharpley F, Rezak T, et al. Treatment of IgM-associated immunoglobulin light-chain amyloidosis with rituximab-bendamustine. *Blood*. 2018 Aug;132(7):761–4.
- 51 Milani P, Schönland S, Merlini G, Kimmich C, Foli A, Ditttrich T, et al. Treatment of AL amyloidosis with bendamustine: a study of 122 patients. *Blood*. 2018 Nov;132(18):1988–91.

- 52 Sanchorawala V, Palladini G, Kukreti V, Zonder JA, Cohen AD, Seldin DC, et al. A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis. *Blood*. 2017 Aug;130(5):597–605.
- 53 Dispenzieri A, Kastritis E, Wechalekar AD, Schönland SO, Kim K, Sanchorawala V, et al. Primary Results from the Phase 3 Tofacitinib-AL1 Trial of Ixazomib-Dexamethasone Versus Physician's Choice of Therapy in Patients (Pts) with Relapsed/Refractory Primary Systemic AL Amyloidosis (RRAL). *Blood*. 2019;134 Supplement_1:139.
- 54 Cohen OC, Sharpley F, Gillmore JD, Lachmann HJ, Sachchithanatham S, Mahmood S, et al. Use of ixazomib, lenalidomide and dexamethasone in patients with relapsed amyloid light-chain amyloidosis. *Br J Haematol*. 2020. DOI: 10.1111/bjh.16401.
- 55 Leung N, Thomé SD, Dispenzieri A. Venetoclax induced a complete response in a patient with immunoglobulin light chain amyloidosis plateaued on cyclophosphamide, bortezomib and dexamethasone. *Haematologica*. 2018 Mar;103(3):e135–7.
- 56 Ghilardi G, Stussi G, Mazzucchelli L, Röcken C, Rossi D, Gerber B. Venetoclax plus daratumumab induce hematological CR and organ response in an AL amyloidosis patient with t(11;14). *Amyloid*. 2019 Sep;26(3):173–4.
- 57 Gran C, Borg Bruchfeld J, Ellin F, Nahi H. Rapid Complete Response to Single-Agent Bcl-2 Inhibitor Venetoclax in a Heart-Transplanted Patient with Triple Refractory Immunoglobulin Light-Chain Amyloidosis. *Acta Haematol*. 2020. DOI: 10.1159/000504355.
- 58 Sanchorawala V, Sarosiek S, Schulman A, Mistark M, Migre ME, Cruz R, et al. Safety, Tolerability, and Response Rates of Daratumumab in Relapsed AL Amyloidosis: Results of a Phase II Study. *Blood*. 2020. DOI: 10.1182/blood.2019004436.
- 59 Roussel M, Merlini G, Chevret S, Arnulf B, Stoppa AM, Perrot A, et al. A prospective phase II of daratumumab in previously treated systemic light chain amyloidosis (AL) patients. *Blood*. 2020. DOI: 10.1182/blood.2019004369.
- 60 Kimmich CR, Terzer T, Benner A, Dittrich T, Veelken K, Carpinteiro A, et al. Daratumumab for systemic AL amyloidosis: prognostic factors and adverse outcome with nephrotic range albuminuria. *Blood*. 2020. DOI: 10.1182/blood.2019003633.
- 61 Lecumberri R, Krsnik I, Askari E, Sirvent M, González-Pérez MS, Escalante F, et al. Treatment with daratumumab in patients with relapsed/refractory AL amyloidosis: a multicentric retrospective study and review of the literature. *Amyloid*. 2020. DOI: 10.1080/13506129.2020.1730791.
- 62 Merlini G, Ascarì E, Amboldi N, Bellotti V, Arbustini E, Perfetti V, et al. Interaction of the anthracycline 4'-iodo-4'-deoxydoxorubicin with amyloid fibrils: inhibition of amyloidogenesis. *Proc Natl Acad Sci USA*. 1995 Mar; 92(7):2959–63.
- 63 Gianni L, Bellotti V, Gianni AM, Merlini G. New drug therapy of amyloidosis: resorption of AL-type deposits with 4'-iodo-4'-deoxydoxorubicin. *Blood*. 1995 Aug;86(3): 855–61.
- 64 Cardoso I, Saraiva MJ. Doxycycline disrupts transthyretin amyloid: evidence from studies in a FAP transgenic mice model. *FASEB J*. 2006 Feb;20(2):234–9.
- 65 Diomedea L, Rognoni P, Lavatelli F, Romeo M, del Favero E, Cantù L, et al. A Caenorhabditis elegans-based assay recognizes immunoglobulin light chains causing heart amyloidosis. *Blood*. 2014 Jun;123(23):3543–52.