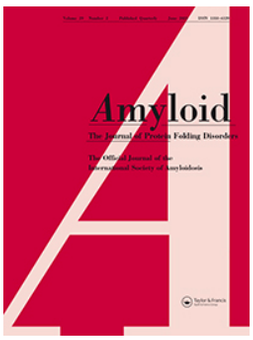

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GUIDELINE ARTICLE

Guidelines for non-transplant chemotherapy for treatment of systemic AL amyloidosis: EHA-ISA working group

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ABSTRACT

Background: This guideline has been developed jointly by the European Society of Haematology and International Society of Amyloidosis recommending non-transplant chemotherapy treatment for patients with AL amyloidosis.

Methods: A review of literature and grading of evidence as well as expert recommendations by the ESH and ISA guideline committees.

Results and Conclusions: The recommendations of this committee suggest that treatment follows the clinical presentation which determines treatment tolerance tempered by potential side effects to select and modify use of drugs in AL amyloidosis. All patients with AL amyloidosis should be considered for clinical trials where available. Daratumumab-VCD is recommended from most untreated patients (VCD or VMDex if daratumumab is unavailable). At relapse, the two guiding principles are the depth and duration of initial response, use of a class of agents not previously exposed as well as the limitation imposed by patients' fitness/frailty and end organ damage. Targeted agents like venetoclax need urgent prospective evaluation. Future prospective trials should include advanced stage patients to allow for evidence-based treatment decisions. Therapies targeting amyloid fibrils or those reducing the proteotoxicity of amyloidogenic light chains/oligomers are urgently needed.

Abbreviations: ACE: Angiotensin Converting Enzyme Inhibitors; AL: Amyloidosis light chain; ASCT: Autologous Stem cell transplant; BCL-2: B-cell lymphoma gene 2; BCMA: B Cell Maturation Antigen; BDR: Bendamistine-Dexamethasone-Rituximab; BEAM: BCNU, Etoposide, Cytarabine, Melphalan; BiTE: bispecific T-cell engager; CAR-T: Chimeric antigen receptor T-Cell; Co2: Carbon di-oxide; CR: Complete Resposne; CRS: Cytokine release syndrome; CTCAE: Common Terminology Criteria for Adverse Events; cTn: cardiac troponin; CyBorD: Cyclophosphamide-Bortezomib-Dexamethasone; dFLC: difference between the involved and uninvolved light chain; dLCO: diffusion capacity for carbon monoxide; DRC: Dexamethasone-Rituximab-Cyclophosphamide; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filteration rate; EHA: European Haematology Association; EMN: European Myeloma Network; FLC: Free light chain; GI: Gastrointestinal; HR: haematologic response; I C d: Ixazomib-cyclophosphamide-dexamethasone; I M iD: immunomodulatory agent; iFLC: involved free light chain; IRD: Ixazomib-lenalidomide-dexamethasone; ISA: International Society of Amyloidosis; IV: Intravenous; LCDD: Light Chain deposition disease; locAL: Localised AL; LVEF: Left ventricular ejection fraction; m Ab: monoclonal antibody; Mdex: Melphalan-Dexamethasone; MOD-PFS: Major organ deterioration progression free survival; MRD: Minimal Residual Disease; MTD: Maximum Tolerated Dose; MYD-88: Myeloid differentiation primary response 88; NHL: Non-Hodgkins Lymphoma; NT-proBNP: N-terminal fragment of pro-brain natriuretic peptide; PFS: progression free survival; PI: proteasome inhibitor; PR: Partial Response; SAP: Serum Amyloid P Component; SLAMF7: Signalling Lymphocyte Activation Molecule Family; SQ: subcutaneous; US: United States of America; VCD: Velcade-cyclophosphomide-dexamethasone; VGPR: Very Good Partial Response; VMDex: Velcade-Melphalan-Dexamethasone; WM: Waldenstrom's Macroglobulinaemia

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Introduction

The current treatment paradigm for AL amyloidosis aims to reduce the production of amyloidogenic immunoglobulin light chain by suppressing the underlying plasma cell clone with a view to reducing the availability of the toxic amyloid precursor and to halting amyloid deposition, allowing for gradual tissue regression of amyloid deposits leading to organ response and improved survival. Disease staging using criteria for cardiac staging based on Mayo clinic staging system (European modification of Mayo 2004 (stages I, II, IIIa and IIIb) [1] and Mayo 2012 update incorporating additional serum free light chains (stage I-IV)) [2] as well as renal staging system from Palladini and colleagues is crucial at baseline for risk stratification. The depth of haematologic response is directly associated with outcomes in AL amyloidosis [3]. Therapy for AL amyloidosis has been adopted from regimes studied in the treatment of multiple myeloma along with supportive measures to manage the amyloid-related complications. Lately, prospective trials studying novel regimes in AL have been completed and are an area of increasing interest to academia and industry. Daratumumab with cyclophosphamide-bortezomib-dexamethasone became the first formally licenced treatment for AL amyloidosis in 2021. The advantage of a particular cytotoxic treatment must be balanced against the patient's baseline organ function, which can be significantly compromised because of amyloid deposition. Standardised assessment of disease status is key to inform treatment intensity and choice.

All patients with symptomatic systemic AL amyloidosis with visceral organ involvement, significant soft tissue involvement, coagulopathy or neuropathic involvement should be considered for early treatment. The benefits of chemotherapy for patients with a monoclonal gammopathy and isolated amyloid deposits on a bone marrow biopsy or in the carpal tunnel in absence of any other end organ involvement remain unclear but, due to a very high risk of systemic progression, such patients need close long-term follow up. Localised AL amyloidosis, affecting a single organ site in absence of any other systemic deposition occurring often in the upper respiratory, urogenital and gastrointestinal tracts, the skin and the orbit, is a relatively indolent disorder needing local (usually surgical) interventions and chemotherapy is generally not indicated [4].

Methodology

The objective of this guideline is to provide healthcare professionals with clear guidance on the management and investigation of patients with AL amyloidosis. A PubMed search was conducted including clinical trials in AL amyloidosis and papers or reviews where AL amyloidosis was the major focus. Relevant meeting abstracts were also included. All papers were evaluated according to the GRADE criteria. Levels of evidence and grades of recommendation are based on the GRADE system (http://www.gradeworkinggroup.org). Expert consensus was used were there were limited published data.

The draft guideline was reviewed and agreed by the members of the writing group and approved by the board of the International Society of Amyloidosis and European Haematology Association Guidelines committee. The treatment scenario is rapidly changing and these guidelines will be considered current until any publication of update/review or three years from the date of current publication (whichever is earlier).

Goals of treatment, assessing and monitoring treatment response

The international society of amyloidosis (ISA) has published response criteria for AL amyloidosis [3] and there were recently clarified [5] (Table 1). Multiple organ biopsies to assess amyloid regression or progression have no significant

Table 1. Updated criteria for organ response and progression in AL amyloidosis [108–110].

Organ	Response	Progression
Heart	NT-proBNP response (>30% and > 300ng/L decrease in patients with baseline NT-proBNP ≥ 650 ng/L) OR NYHA class response (≥2 class decrease in subjects with baseline NYHA class 3 or 4)	NT-proBNP progression (>30% and > 300 ng/L increase)* OR cTn progression (≥33% increase) OR Ejection fraction (EF) progression (≥10% decrease in EF)
Kidney	30% decrease of 24-hr urine protein or drop below 0.5 g/day (urine protein must be > 0.5 g/day pretreatment). Estimated glomerular filtration rate must not worsen by 25% over baseline.	25% worsening of estimated glomerular filtration rate
Liver	50% decrease in abnormal alkaline phosphatase value Decrease in liver size radiographically at least 2 cm	50% increase of alkaline phosphatase above the lowest value
Peripheral nervous system	Improvement in electromyogram nerve conduction velocity (rare)	Progressive neuropathy by electromyography or nerve conduction velocity
Definitions for Haematologic response in AL amyloidosis		
Response categories	**Definitions**	
Complete response	Both criteria must be met: • Absence of amyloidogenic light chains (either free and/or as part of a complete immunoglobulin) defined by negative immunofixation electrophoresis of both serum and urine • Either a FLC ratio within the reference range or the uninvolved FLC concentration is greater than involved FLC concentration with or without an abnormal FLC ratio	
Very good partial response	dFLC concentration < 40 mg/L	
Partial response	dFLC decrease > 50% compared to baseline	
No response	All other patients	

NT-proBNP: N-terminal pro-Brain Natriuretic Peptide; NYHA: New York Heart Classification; FLC: free light chain ratio; dFLC: difference between the involved and uninvolved light chains; cTn: cardiac troponin T; EF: ejection fraction.

value, are frequently misleading and potentially dangerous. Response in AL amyloidosis involves assessment of the direct impact of chemotherapy on the clone and, an indirect effect of improvement in organ function based on the *a priori* organ damage (an "organ response") as well as depth of haematologic response achieved. Although the deeper the haematologic response, the greater is the likelihood of organ responses, there may be a discrepancy between the haematologic response and organ response. The present criteria define organ response in a binary fashion (response/no response). Efforts are ongoing to develop a composite response model which not only grades the extent of the organ response but also incorporates the haematologic response.

Whilst organ response is the goal of treatment and, since none of available agents can influence this directly, achieving a very good partial haematologic response (VGPR) was considered as the "goal" of treatment in AL amyloidosis. However, the ISA criteria clearly show that a complete response (CR) is associated with superior outcomes [3] and, lately, single centre studies shown that reaching very low free light chain levels after treatment (difference between involved and uninvolved light chains (dFLC) or involved free light chain (iFLC)) is also predictive of better outcomes [6–9]. These guidelines would suggest achieving a complete haematologic response is the goal of treatment in AL amyloidosis, ideally associated with iFLC $<$ 20 mg/L or dFLC $<$10 mg/L. Haematologic response should be evaluated at least monthly (more frequently in advanced patients) and treatment modification is considered early if the patient does achieve progressive FLC response within the initial cycles (if the response following 2 cycles if $\leq$ partial response (PR) or following 3 cycles $<$ VGPR and no organ response has occurred) [10]. An algorithm to help treatment modification based on depth of response has been published [11].

There is mounting evidence indicating that undetectable minimal residual disease (MRD) is associated with higher rates of organ responses and significant reduction of the risk of haematologic relapse [12,13]. However, this endpoint has not been evaluated prospectively and, as yet, cannot be proposed as the goal of therapy in all patients; no recommendations can be made on optimal timing of assessment, optimal evaluation method and clinical decision making based on detection of MRD.

Recommendations on goals of clone directed treatments in AL amyloidosis:

- *Goal of treatment is to achieve a complete haematologic response (Grade B, Level IIb) with iFLC $<$20 mg/L or dFLC $<$10 mg/L (Grade B; Level III)*
- *Patients achieving less than a very good partial response by cycle 3 or less than a partial response by cycle 2 should be considered for treatment modification (Grade C; Level IV)*

Supportive care

A multidisciplinary approach to management is crucial with involvement from cardiologists, nephrologists, neurologists, gastroenterologists (depending on the type/extent of organ involvement) in addition to the treating haematologists [14]. Stringent supportive therapy is critical to survival of patients. In cases with renal or cardiac involvement, the key element is meticulous fluid balance. It is important to avoid commonly used drugs for heart failure (like ACE inhibitors, beta blockers or calcium channel blockers) which may worsen symptoms [15]. Patients presenting with severe nephrotic syndrome can have substantial urinary loss of proteins, such as albumin (edema and intravascular volume depletion), immunoglobulins (increasing risk of infections), loss of antithrombin-III and activation of coagulation factors (increased risk of thrombosis) – each needing specific clinical review and intervention if appropriate. Proactive identification and management of cardiac arrhythmias as well as judicious but early use of anticoagulants in patients with atrial fibrillation, poor atrial function as well as those with severe nephrotic syndrome, are important. Patient education in monitoring blood pressure and fluid status can help. There are limited data on use of supportive care measures in AL amyloidosis [14] and these recommendations are based on expert consensus opinion.

Treatment of newly diagnosed patients with AL amyloidosis

Treatment of AL amyloidosis is risk adapted. The choice of regime, agent and intensity is dictated by the degree of organ involvement, the performance status, age, and bone marrow findings. The primary decision is whether a patient is a candidate for an autologous stem cell transplant (ASCT) as part of the upfront therapy, or combination chemotherapy without ASCT. The ISA ASCT guidelines discuss the criteria for stem cell transplantation in detail [16]. Apart from the patients fulfilling the criteria outlined in the ISA-ASCT guidelines (and briefly below), all other patients are treated with chemotherapy-based approaches. With increasing effectiveness of chemotherapy regimens, especially incorporating daratumumab upfront, the current role of ASCT in newly diagnosed AL remains to be clarified. However, in patients with AL amyloidosis with underlying symptomatic myeloma, and in patients with IgM-AL amyloidosis, ASCT remains an important part of first line therapy.

Selection of candidates for ASCT (*refer for details to the ISA ASCT guideline* [16])

The eligibility criteria for ASCT varies from centre to centre. Only ~20% of newly diagnosed patients are eligible to receive this intensive form of treatment. Selection criteria for treatment with ASCT have required a confirmed tissue diagnosis of AL amyloidosis with end organ damage, age 18–70 years, and minimum measures of performance status (Eastern Cooperative Oncology Group (ECOG) 0–2), cardiac function (left ventricular ejection fraction (LVEF) $>$40%), pulmonary function (O_2 saturation $>$95% on room air, diffusing capacity of the lungs for carbon monoxide (DLCO) $>$ 50% of predicted, absence of medically refractory

pleural effusions), hepatic function (direct bilirubin <2 mg/dL), renal function (estimated glomerular filtration rate (eGFR) >30 ml/min/1.73m^2) and hemodynamic stability (baseline supine systolic blood pressure >90 mm Hg). Patients on haemodialysis or peritoneal dialysis for renal failure are not excluded if other eligibility criteria are met. Cardiac biomarker staging system can also define risk of treatment-related complications while undergoing ASCT. Elevated cardiac troponin T levels (>0.06 ng/ml) and N-terminal fragment of pro-brain natriuretic peptide (NTproBNP) (>5000 pg/mL; in practice, a lower NT-proBNP threshold may be considered) are associated with poor survival while undergoing ASCT.

Non-transplant approaches

Alkylating agents

Melphalan and cyclophosphamide (plus corticosteroids) are active against plasma cell clones and are mostly used as part of triplet combinations with newer agents. Melphalan plus dexamethasone (MDex) is a relatively safe therapy for transplant-ineligible patients with haematologic response rates up to 76% [17], but is less effective than when combined with bortezomib (BMDex) [18]. Use of oral melphalan and dexamethasone without incorporation of novel agents is now considered suboptimal in majority of patients.

Proteasome inhibitors (PIs)

Clonal plasma cells in AL amyloidosis are particularly sensitive to PIs because of their dependence on proteasome integrity to cope with the proteotoxic stress caused by the misfolded light chains [19]. Targeting the proteasome has been a highly effective strategy in AL amyloidosis. Bortezomib, either as single agent [20], with dexamethasone [21,22] or as part of a triplet, is highly active. It is administered subcutaneously, usually once weekly, combined with dexamethasone and an alkylating agent. Bortezomib-containing regimens are considered as the primary therapy for AL amyloidosis in most centres in Europe, the US and Asia-Pacific.

Bortezomib-Cyclophosphamide-Dexamethasone (VCD or CyBorD) is most commonly used regimen and a weekly bortezomib protocol is preferred (there is no specific need for weeks' treatment break each cycle ("off week")) [6,23–27]. Overall hematological response rates with VCD/CyBorD range between 60% and 65%, with CRs in the range of 18–25% in the larger series [6,23]. This regimen is moderately well tolerated, does not cause significant myelosuppression, may be administered with cyclophosphamide orally or intravenous (IV) and does not require dose adjustments for renal impairment. There is a suggestion that VCD/CyBorD may be less effective in patients harbouring a plasma cell clone with chromosomal translocation *t*(11;14) [28,29].

Bortezomib combined with oral melphalan and dexamethasone (BMDex) was compared to MDex in a prospective randomised study in newly diagnosed transplant ineligible patients with disease Mayo stage I–IIIA [18]. BMDex treated patients achieved an 81% hematological response rate at 3 months compared to 57% in the MDex arm. This is the only therapy in AL amyloidosis that has shown a survival improvement, mainly in patients with a mild cardiac disease (Mayo Clinic stage II) in a prospective randomised study with contemporary regimens. Retrospective data suggest that BMDex may be able to overcome the disadvantage of bortezomib in patients harbouring *t*(11;14) but further validation is needed for recommending this [28,29]. The melphalan dose needs renal adjustment, myelotoxicity may be more pronounced than with cyclophosphamide and late effects such as myelodysplastic syndromes can occur. Neuropathy is the primary and limiting toxicity of bortezomib. A signal of cardiotoxicity may also exist with bortezomib; atrial arrhythmias may be more frequent with intravenous (IV) administration than with subcutaneous (SQ) bortezomib [30]. Bortezomib needs to be used with caution in patients with significant lung disease due to a small risk of pulmonary toxicity [31].

Ixazomib is a second-generation PI, with oral administration and lower neurotoxicity compared to bortezomib. A phase III randomised study evaluated Ixazomib with dexamethasone vs physician choice in patients with relapsed AL amyloidosis. Although the first primary endpoint of overall haematologic response rate was not met, Ixazomib–dexamethasone prolonged time to vital organ deterioration and mortality, progression free survival (PFS) and time to subsequent therapy vs physician's choice [32]. In a small phase I/II study, Ixazomib combined with cyclophosphamide and dexamethasone (ICd) was safe and well tolerated in newly diagnosed AL amyloidosis patients and induced ≥ VGPR in 39% [33]. In a phase 2 study from Mayo Clinic, ICd followed by ixazomib maintenance was given in 35 patients. After a median of 4 cycles, overall haematologic response was 57%, including CR in 14% and VGPR in 26%; however, the most common reason to move off study was institution of alternate therapy in 63% of patients [34]. In small study from China [35], 25 newly diagnosed patients received ixazomib 4 mg with low-dose (10 mg) dexamethasone; after a median of 4 cycles of therapy, 70.8% achieved a haematologic response, including 43% CR and 21% VGPR. Most common severe toxicities included thrombocytopenia and diarrhoea.

Carfilzomib is an irreversible second-generation PI which has shown improved efficacy compared to bortezomib in relapsed/refractory but not in newly diagnosed, transplant ineligible patients with myeloma. The known cardiovascular and renal toxicity of carfilzomib limits its use in patients with AL amyloidosis when other options are available. In a small series ($N = 5$) carfilzomib was safe and active in newly diagnosed patients with peripheral neuropathy [36]. A prospective phase 1 study has reported on safety of carfilzomib-thalidomide-dexamethasone in relapsed AL amyloidosis [37].

Immunomodulatory agents (IMiDs)

IMiD's are useful in treatment of AL amyloidosis and form an important part of the therapeutic armamentarium. However, clonal responses to IMiDs tend to be slow in most patients with AL amyloidosis. Thalidomide is associated with significant neurological and GI toxicity, low doses are used and is no longer widely prescribed [38]. Lenalidomide is poorly tolerated at the full 25 mg daily dose in AL amyloidosis and all patients should start with significant dose reduction (escalation based on tolerance). When combined with MDex or cyclophosphamide/dexamethasone in previously untreated patients, at doses of 15 mg daily or lower, haematologic response rates of 46–60% are seen but with low CR rates [39–41]. Common lenalidomide-associated toxicities in patients with AL amyloidosis, include skin rashes, thrombotic complications, infections, fatigue and deterioration of renal function. Pomalidomide has a safer renal profile and is, perhaps, better tolerability in patients with AL amyloidosis compared to lenalidomide; studies in the first line are eagerly awaited [42,43]. Use of IMiDs is associated with an increase in NT-proBNP, which often is transient, but can make assessment of cardiac response challenging task. The upfront combination of bortezomib and low dose lenalidomide was reported in a small study with high haematologic response rates (89% on intent to treat, including CR in 32% and VGPR in 57%), however, toxicity was also significant [41]. A similar combination with pomalidomide, bortezomib and dexamethasone in newly diagnosed patients was also associated with toxicity and early mortality (but unclear if disease or treatment related) [44].

Monoclonal antibodies

Daratumumab is an anti-CD38 monoclonal antibody, with substantial single activity in patients with relapsed/refractory AL amyloidosis [45–47], and in combination with bortezomib-based therapy in newly diagnosed patients.

In the phase III ANDROMEDA study, subcutaneous daratumumab plus VCD was compared to 6 cycles of standard VCD in newly diagnosed stage I–IIIA patients; daratumumab continued for up to 18 months in the dara-VCD arm, after the completion of initial 6 cycles [48]. Daratumumab-VCD combination improved CR rates (the primary end point of the study) to 53% vs. 18% for VCD. Overall haematologic response rates were also significantly higher (92% vs 77%), as well as $\geq$ VGPR rates (79% vs 49%); with similar findings in patients with *t*(11;14) and those with cardiac stage III disease (although the study was not powered for these end points). At 6 months, organ response rates were also higher in the daratumumab-VCD arm (cardiac: 42% vs 22%; renal: 53% vs 24%) which improved at 18 months in the daratumumab-VCD arm to 53% and 58% respectively with no change in the control arm [49]. Early mortality was similar between groups and long term survival outcomes have not yet been evaluated. A study specific end-point (Major Organ Deterioration-progression free survival (MOD-PFS)), defined as a composite of cardiac or renal failure, haematologic progression or death, was improved in the daratumumab-VCD arm, driven primarily by the lower rates of haematologic progressions, at this stage of follow up. Regarding the toxicity of this new combination, there was an increase in infection rates but no clear signal of cardiac toxicity was observed.

Treatment choice

For patients who are ineligible for high dose therapy (*see the high dose therapy guideline*) and no available option of a clinical trial, a combination of daratumumab-VCD is the preferred regimen, if daratumumab is available. If daratumumab is not available, then a bortezomib-based triplet combination, either VCD or BMDex, are primary options. BMDex and VCD have not been compared prospectively limiting evidence-based recommendations. By expert consensus, VCD is the preferred regimen in most patients because it is easy to administer on an outpatient basis, with either oral or IV cyclophosphamide; may be preferable in patients with moderate or severe reduction of eGFR and/or heavy hypoalbuminemia and in those with potentially reversible contraindications to stem cell transplant. BMDex may have a role in selected patients where ASCT is unlikely to be an option at presentation or later in the disease. Melphalan needs dose adjustment when eGFR is below 30 ml/mi/1.73 m^2. Bortezomib and dexamethasone doses need to be adapted to cardiac stage, presence of autonomic/peripheral neuropathy, fluid retention status and patient's functional status.

Optimal duration of therapy has not been evaluated formally. Expert consensus suggests treatment is given for at least two cycles beyond best response. For patients with at least VGPR after 3 cycles, depending on the treatment tolerance, it is reasonable to continue for a total of 6–8 treatment cycles as depth of response can improve.

Recommendations for upfront treatment:

Patients without significant neuropathy:

- *Cardiac Stage I-IIIa: Dara-CyBorD (preferred)(Grade A; Level 1a); alternative CyBorD (Grade B; Level IIa) or VMDex (Grade A; Level 1a)*
- *Cardiac Stage IIIb: Dose modified Dara-CyBorD (Grade C; Level IV) or single agent daratumumab (Grade B; Level III); alternative dose modified CyBorD or VMDex (Grade C; Level IV)*

Maintenance therapy

There is limited data on maintenance therapy in AL amyloidosis. In the ANDROMEDA study, patients treated with Daratumumab-VCD received monthly daratumumab for up to 24 cycles from start of therapy (18 months maintenance); however, patients were not randomised to receive maintenance or not and the data from this part of the study are not available yet. Patients who have amyloidosis on background of symptomatic myeloma are likely to benefit from the use of maintenance therapy as per the recommendations for multiple myeloma. For all other patients with AL

amyloidosis, however, no recommendation can be made given the lack of data but there may be a role in those with persistent clonal disease (less than CR or CR with persistent MRD) and persistent organ dysfunction.

Recommendation:

- *Routine maintenance not recommended (Grade C; Level IV).*

Consolidation therapy

For eligible patients' high dose melphalan may be used as consolidation after less than a complete response to chemotherapy, considering that complete responses are often very long lasting in AL amyloidosis and that high dose melphalan only obtains 16% of complete response in patients refractory to induction treatment; however, in non-ASCT eligible patients, there is limited data regarding the role of consolidation. In a small series in patients with AL ($N = 19$) or light chain deposition disease (LCDD) ($N = 6$) who had not achieved a CR after standard bortezomib-based therapy, consolidation with a short course of daratumumab (4 doses, one month) improved response to CR in 8 (32%) patients, including 5 (20%) patients that became also MRD negative [50]. The role of consolidation treatment with an alternative chemotherapy regime in those achieving a VGPR but not a CR has not been studied. However, the availability of effective low toxicity treatment like daratumumab is changing the treatment paradigm in AL amyloidosis, with the more frequent search for a complete haematologic response. In those patients with no organ response or organ progression despite reaching a VGPR or CR with persistent MRD, there may be a role for further treatment to improve the depth of response.

Recommendation:

- *Routine consolidation not recommended (Grade C; Level IV)*
- *Consolidation treatment may be considered patients with VGPR or CR with persistent MRD and no organ response (Grade C; Level IV)*

Special populations

Stage IIIB patients

Anti-clonal therapy alone may not suffice for such patients, even when haematologic response is rapid, as early mortality may be as high as 50% following therapy initiation [1]. Close collaboration with the heart failure clinic is mandatory, and cardiac transplantation should be discussed for younger patients, especially those with isolated cardiac involvement. Immediate treatment initiation is crucial. Dose modification of bortezomib and/or dexamethasone or sequential introduction of drugs should be considered as appropriate [51]. Daratumumab, if available, is proposed as the preferred option, even starting as single agent;preliminary data of an ongoing European phase II trial show early and deep haematologic responses and encouraging improvement in survival [52]. Intravenous daratumumab may be given in divided doses to reduce fluid volume but the subcutaneous formulation is preferred. Close monitoring is needed and inpatient treatment administration is advised. The advantage of initiating treatment with continuous cardiac monitoring is unclear. Addition of a third agent to bortezomib-dexamethasone may accelerate haematologic response: cyclophosphamide and melphalan are usually well tolerated and daratumumab is, again, preferred. IMiDs are associated with significant toxicity in these patients and should be avoided unless there are contraindications to bortezomib and no access to daratumumab.

Recommendations:

- *Dose modified Dara-CyBorD (Grade C; Level IV) or single agent daratumumab (Grade B; Level III); alternative dose modified CyBorD or VMDex (Grade C; Level IV)*

Patients with neuropathy

Dose reduced bortezomib-based therapy may be used for patients presenting with mild neuropathy. Daratumumab in addition to bortezomib or as single agent is preferred, if available. For patients with severe neuropathy, bortezomib should be avoided as first option and other treatments such as MDex, lenalidomide-based regimes, cautious once weekly carfilzomib-dexamethasone in the absence of advanced cardiac disease or daratumumab-based regimens should be considered, depending on the availability of these agents. The role of Ixazomib in patients with neuropathy remains to be clarified but can be cautiously considered in selected cases. In absence of other options in patients not achieving a haematologic response, cautious bortezomib may be given, with close monitoring of the neuropathy.

Recommendation:

- *Single agent daratumumab or Lenalidomide-Dexamethasone or oral melphalan-dexamethasone or Carfilzomib-Dex or Venetoclax are all possible options (Grade C; Level IV)*
- *Single agent daratumumab is the preferred option (Grade C; Level IV)*

Patients with bleeding

Standard therapy should be used for these patients with careful monitoring to avoid thrombocytopenia, which could increase the risk of major, clinically significant bleeding. Replacement with clotting factor concentrates, as indicated, may be considered. In patients with factor X deficiency and life-threatening bleeding, activated factor VIIa may have role. IMiDs need careful assesement in patients at high bleeding risk due to complexity of balancing risks of bleeding vs. clotting and challenge in use of thromboprophylaxis. The anti-fibrinolytic agent, tranexamic acid, may be used to help decrease the rate of bleeding if there is no

prothrombotic risk factors (like severe nephrotic syndrome or history of ischaemic heart disease or stroke).

Patients with advanced liver dysfunction

Patients presenting with high bilirubin have a particularly poor prognosis in the absence of deep haematologic response, and are challenging to manage since many drugs that undergo hepatic metabolism needing substantial dose adjustments. Dose modification for bortezomib in liver dysfunction remains poorly studied. Conversely, cases of bortezomib-induced liver toxicity have been reported, but is not considered as a hepatotoxic drug; close monitoring is advised. Cyclophosphamide is metabolised and activated in the liver but its metabolites can also cause liver toxicity. Daratumumab has not been tested in patients with liver dysfunction and there is limited data on potential liver toxicity although it is considered as an unlikely cause of clinically apparent liver injury. Lenalidomide has been associated with rare cases of severe hepatotoxicity although mild transaminitis is not uncommon. Daratumumab with steroids may be preferred given the low potential for hepatotoxicity but there is limited data.

Patients requiring dialysis

Being on dialysis is *per se* not an indication for a specific regime choice but all drugs used require renal dose modification. Bortezomib generally does not need dose adjustment but it should administered after dialysis. Standard VCD has been used for several years in the management of patients with acute or chronic renal failure due to plasma cell disorders, either myeloma or AL amyloidosis or other monoclonal gammopathy related diseases. Melphalan requires dose adjustments and may be associated with unpredictable haematologic toxicity in patients with severe renal dysfunction. Among IMiDs, only lenalidomide requires dose modifications according to eGFR/CrCl; these are not necessary for pomalidomide or thalidomide. Daratumumab can be safely administered in patients with severe renal dysfunction or those undergoing dialysis, based on retrospective data from patients with AL amyloidosis or prospective data from myeloma patients. Retrospective data in relapsed/refractory AL have suggested that in patients with heavy proteinuria daratumumab may be less effective due to loss in urine [53] and this may also be a problem with other monoclonal antibody-based treatments in AL. PK data from the ANDROMEDA cohort suggests daratumumab kinetics were similar to that seen in multiple myeloma although specific analysis in patients with heavy proteinuria is not available [54]. When used intravenously, it may should be administered in a smaller fluid volume.

IgM related amyloidosis

In most of these cases, a B-cell non-Hodgkin's lymphoma (NHL) and not a plasma cell is the culprit clone. Often lymphoplasmacytic clones are present but the type of monoclonal cells in the bone marrow should be carefully assessed as a study in 70 patients with IgM amyloidosis showing that 16 (23%) had pure plasma cell neoplasm with a $t(11;14)$ in 60% of cases whilst most of the patients with a lymphoplasmacytoid clone had MYD-88 mutations (presence of which may help the distinction) [55]. Regimens designed for NHL/Waldenström's macroglobulinaemia (WM), targeting mature B-cells, are preferred for those with a lymphoplasmacytic neoplasm. Rituximab-based regimens are the mainstay of therapy, based mostly in the experience from treatment of WM. Rituximab with bendamustine has been used extensively in IgM-AL [56,57]. Combinations with rituximab and bortezomib (such as bortezomib with DRC or BDR [58–60]) may be another options, but these have not been compared prospectively. Responses to Ibrutinib appear modest. It may be considered as a treatment in selected patients without other treatment options for an underlying lymphoplasmacytic or small lymphocytic clone; however, limited experience in AL amyloidosis suggested that there may be potential cardiotoxicity of this drug and it appears to be poorly tolerated [61]. The retrospective analysis of 38 patients treated with ASCT showed a deep haematologic response ($\geq$VGPR) in 76% of patients with renal and cardiac responses in 65% and 60% of patients, respectively. Treatment-related mortality was 5% [62]. IgM-related amyloidosis is considered one of the indications for ASCT due to poor responses with standard treatments and limited treatment options (compared to non-IgM AL amyloidosis) at relapse. There is limited data on conditioning regimens for ASCT but consideration to using BEAM (BCNU, Etoposide, Cytarabine, Melphalan) in younger fitter patients with lymphoplasmacytoid clones may be beneficial.

Recommendation:

- *Preferred treatment: Rituximab-Bendamustine (Grade B; Level IIb) or ASCT (Grade B, Level IIb)*
- *Alternatives: Rituximab-bortezomib-Dex or Rituximab-Cyclo-Dex or CyBorD or Ibrutinib(±Ritux) (Level C; Grade IV)*

Treatment of relapsed disease

Most patients with AL amyloidosis will relapse after initial first line treatment and ISA has defined relapse criteria in AL amyloidosis. However, these were defined when risks of progression and light chain proteotoxicity were less well understood. Patients often relapse slowly with progressive light chain increase which may or may not be associated with worsening end organ dysfunction at the onset of relapse. The Mayo clinic group showed that patients with relapse and end organ dysfunction have poorer outcomes than those treated just for serological progression [63]. Palladini et al. put forward the concept of patients with "high-risk dFLC progression" [64] which was defined as a dFLC of >20 mg/L, a level >20% of baseline value, and a >50% increase from the value reached at best response and is conceptually attractive. However, both arguments for

advocating early therapy at clonal relapse to prevent organ progression [65] and cautioning against over-enthusiastic resumption of chemotherapy in frail patients at the first sign of clonal relapse [66] are both valid in this patient population. Formal studies for the threshold iFLC/dFLC levels for re-starting chemotherapy remain limited. Thus, it is reasonable to consider therapy when the dFLC has reached 50% of the diagnostic level in a patient with limited vital organ involvement but most patients who present with significant end organ dysfunction (cardiac, renal or autonomic), application of the "high-risk" dFLC-progression is more appropriate. In patients with initial severe cardiac disease, relapse treatment should be rapidly initiated in case of haematologic relapse from complete response.

There are many potential options available for treatment of relapse systemic AL amyloidosis; proteasome inhibitors (PI), monoclonal antibodies (mAb), immunomodulatory therapy (IMIDs), venetoclax, bendamustine, and high dose melphalan with autologous stem cell transplantation (ASCT). The options of patient relapsing or progressing on D-VCD remain unclear. Whilst it is not possible to be prescriptive regarding the optimal sequencing of therapies, the two guiding principles are the depth and duration of initial response, use of a class of agents not previously exposed as well as the limitation imposed by patients' fitness/frailty and end organ damage. For example, prolonged response with bortezomib based regime (with no neuropathy) would encourage re-treatment with a PI, ideally with a different partner for combination. In patients without prior daratumumab exposure, daratumumab based regime may be favoured. Enrolment in clinical trials is encouraged.

Proteasome inhibitors in relapsed AL

Ixazomib

Ixazomib may be useful agent at relapse as demonstrated by the phase 3 TOURMALINE-AL1 study. Although the study did not reach its primary end point, haematologic overall response rate (ORR) was 63% for Ixa-Dex in PI-naïve patients, and 41% in PI-exposed patients. Patients stayed on therapy substantially longer in the Ixa-dex arm compared to physician's choice [32]. It is also tolerated in combination with lenalidomide and dexamethasone (IRD) with median PFS of 17.0 months (95% CI 7.3–20.7 months), improving to 28.8 months (95% CI 20.6–37.0 months) in those achieving CR/VGPR [67]. The weekly oral nature of this treatment is very convenient, and the agent is well tolerated, with minimal neuropathy.

Carfilzomib

There is limited data on carfilzomib. Small studies have demonstrated efficacy. Cohen *et al.* reported their Phase I/II trial of carfilzomib in 28 patients with relapsed/refractory Mayo cardiac stage I or II disease. The 20/36 mg/m^2 biweekly dosing was determined as the maximum tolerated dose (MTD). While the haematologic response rate of 63% is comparable to most other therapies for relapsed/refractory disease, the CR was low at 11%. 20 patients experienced Grade III/IV toxicity (according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0), many cardiac or pulmonary. It has also been reported to be useful with a once weekly schedule in combination with thalidomide and dexamethasone in a phase 1 study [37] with no substantial grade III/IV toxicity and good responses. Overall, there are significant safety concerns with carfilzomib, especially cardiac and renal disease, caution dosing and close monitoring is advised. It may have a role in patients with neuropathic presentation and should be used with once weekly protocol.

Anti-CD38 monoclonal antibodies in relapsed AL

Daratumumab

A number of retrospective and prospective studies have reported high response rates and excellent tolerance for daratumumab in patients with relapsed AL amyloidosis [68,69]. A prospective Phase 2 trial of 40 relapsed/refractory patients receiving daratumumab monotherapy demonstrated haematologic response rate of 59% with VGPR or greater in 44%, typically reached within one cycle [46]. Daratumumab was well tolerated, with no unexpected adverse events, with infection and atrial fibrillation the most commonly report toxicities. The duration of treatment remains to be clearly established. A small retrospective study suggested good responses with daratumumab in combination with lenalidomide and dexamethasone [70].

Isatuximab

Preliminary results of a Phase II study of isatuximab for relapsed disease reported overall haematologic response rate was 77%, with a low CR rate of 3%, but VGPR was 54%, and partial response seen in 20% in 25 patients. The most common reasons for discontinuation were adverse events in 26%.

Immunomodulatory agents in relapse AL

Thalidomide, lenalidomide and pomalidomide have been all been reported in relapsed patients with AL amyloidosis [71]. However, there are no phase III trials in this setting. Thalidomide has significant toxicities and can no longer be considered as an optimal agent for treatment of relapsed AL, unless used due to resource constraints. All IMiD's have a potential to increase NT-proBNP and may worsen renal function [72] – both require close monitoring.

Lenalidomide

Lenalidomide is less well tolerated in AL amyloidosis than in myeloma. A daily lenalidomide dose of 15 mg has been established as the MTD in a phase I/II dose escalation study [73]. Using this lower dose, haematologic response rates around 60% have been reported when combined with cyclophosphamide, and dexamethasone [74,75] although the CR rate has remained disappointingly low. Median time to haematologic response is 3 months. Lenalidomide does not

appear to induce or exacerbate neuropathy in most AL patients, thus lenalidomide-based regimens can be considered for patients with amyloid neuropathy. Like all IMIDs, lenalidomide increases BNP and NT-proBNP levels. This is independent of changes in renal function and FLC causing interference with the assessment of cardiac response.

Pomalidomide

This third-generation immunomodulatory agent has been tested in AL amyloidosis over the last decade [43,76,77], showing in combination with weekly dexamethasone in previously treated patients, a HR rate of 48% with organ responses in 5/33 patients. The most common adverse effects were fatigue and neutropenia. The maximum tolerated dose was confirmed as 4 mg daily (same as the recommended dose in myeloma). A recent real-world analysis of 153 relapsed patient treated with pomalidomide-dexamethasone showed, at the completion of cycle 6, 68 (44%) patients obtained at least partial haematologic response, with 5 complete responses (CR, 3%), 35 very good partial responses (VGPR, 23%) [42].

Bendamustine

Two studies of bendamustine with dexamethasone have suggested good clonal response rates in heavily pre-treated patients, but the significant haematologic toxicity observed prevents routine use of this agent [78]. Its major role remains in patients with IgM related AL amyloidosis.

Recommendation for treatment of relapsed disease:

Proteasome inhibitor Naïve or prolonged response to 1st line PI:

- *CyBorD/VMDex B (Level B; Grade III); Ixazomib-Dex (Grade A; Level Ib); Dara-V(C)D (Level C; Grade IV)*

Proteasome inhibitor exposed Daratumumab Naïve:

- *Single agent daratumumab (Level B; Grade IIb), Dara-V(C)D (Level C; Grade IV), Dara-RD (Level B; Grade III), Isatuximab (Level C; Grade IV)*

Proteasome inhibitor exposed IMiD Naïve:

- *Lenalidomide-Dexamethasone (±cyclophosphamide) (Level B; Grade IIa), Ixazomib-Lenalidomide dexamethasone (Grade B; Level IIb)*

Lenalidomide Refractory:

- *Pomalidomide-Dexamethasone (Level B; Grade IIa), Bendamustine (Level B; Grade IIa)*

Novel anti—plasma cell agents on horizon/off label use

A number of novel anti-plasma cell approaches studies in myeloma are on the horizon for patients with AL amyloidosis.

BCL2 (B-cell lymphoma 2 gene) inhibitors

Patients with *t*(11;14) translocation, a finding noted in approximately 50% of patients with AL amyloidosis, have a dependence of plasma cells on the constitutive activation of the cellular processes related to cyclin D1 activation [79]. The resultant BCL-2 inhibition with this agent removes the anti-apoptotic protective mechanisms leading to preferential killing of affected cells. Agents targeting BCL2 pathway are, hence, of interest in this disease. Venetoclax is the best studied agent and experience in multiple myeloma suggests that this agent has significant activity in patients with the myeloma having *t*(11;14) translocation [80]. Based on clinical trial data in multiple myeloma, this compound has single agent activity but also works in combination with bortezomib and daratumumab; both being important agents in the present management of AL amyloidosis. Retrospective data on the use of Venetoclax in AL amyloid suggests responses are notably deep and durable; and it is well tolerated even in frail patients [81]. There is no prospective data on venetoclax dosing in AL amyloidosis; hence, starting at a low dose and increasing cautiously based on tolerance is important. Prospective data specifically in the AL amyloidosis population is awaited but if the early experience with this agent holds true, it would become a very useful tool in addressing the highly prevalent population of AL amyloidosis patients with the *t*(11;14) abnormality known to have a sub-optimal response to proteasome inhibitors.

Recommendation for patients with t(11;14) translocation:

- *Venetoclax (Grade B; Level III); Venetoclax-Bortezomib-Dexamethasone (Grade C; Level III), Melphalan Dexamethasone (Grade C; Level IV)*

BCMA targeting agents

The B-cell maturation antigen (BCMA) is another cell surface molecule ubiquitously expressed on plasma cell as well as their B-cell progenitors. There have been several unique targeting strategies demonstrating clear anti-plasma cell activity in multiple myeloma [82]. To date, however, the experience specifically in AL amyloidosis is limited. A novel antibody-drug conjugate, Belantamab mafodotin, combines the potent mafodotin toxin with plasma cell targeting anti-BCMA monoclonal antibody [83]. It has demonstrated excellent single agent activity in advanced relapsed and refractory multiple myeloma. Combination studies with various immunomodulating agents and proteasome inhibitors are ongoing. A prospective EMN study (NCT04617925) is examining Belantamab in relapsed AL amyloidosis. An important consideration with this agent is the unique ocular toxicity in the form of keratopathy which has proven to be a challenge in the delivery of this agent. In AL amyloidosis, with the often-lower clonal burden, less frequent and finite dosing strategies built around response adapted approaches may help limit this issue without compromising efficacy.

BCMA has also proven to be an excellent target for chimeric antigen receptor T-cells (CART) and bispecific T-cell engagers (BiTE). There are now numerous products in both these classes with demonstrable anti-plasma cell activity but trials exploring their use in AL amyloid are lacking. The advantages to their use in AL amyloidosis are likely to be the low plasma cell burden with a potential for very deep/durable responses but challenges of cytokine release syndrome (CRS) remain to be overcome in this fragile population.

An additional anti-plasma cell target is CS-1 (SLAMF7). *In vitro* data has suggested that this may be an optimal target particularly in AL amyloidosis as it may be more heavily expressed on the plasma cells giving rise to this disorder [84]. The monoclonal antibody Elotuzumab is being studied specifically in AL amyloidosis. Building on success in multiple myeloma and some notable small case series in AL amyloidosis [85], a prospective phase II study examining elotuzumab, lenalidomide, dexamethasone ± cyclophosphamide is underway (NCT03252600). CS-1 may also prove to be a useful target for CART development in this disease. Pre-clinical data in mice with anti-CS1 directed CART cells has demonstrated this proof of concept but studies in humans are lacking [84]. Again, the potential for deep and durable responses certainly justifies further exploration.

Recommendation:

- *Belantamab Mafodotin (Grade B; Level III)*
- *CAR-T cell or Bispecific antibodies are not recommended outside of clinical trials*

Treatment of localised AL amyloidosis

Localised light chain amyloidosis (locAL) is a rare and heterogeneous disease characterised by the local deposition of amyloidogenic light chains produced by a local B-cell or plasma cell clone but more often has the presenting characteristics of a marginal zone lymphoma [86–88]. The most common involved sites are the airways (larynx, trachea and bronchi) and the lung, the urinary tract, skin and gastrointestinal tract [4,89,90]. These patients do not progress to systemic AL amyloidosis and do not require repeated extensive systemic investigations. Organ involvement may present as a single amyloid lesion (amyloidoma) or multiple localizations across all the anatomical site. LocAL is often asymptomatic and diagnosis can be incidental, especially in the lung [90]. Even if symptoms depend mostly on the site of localisation, clinical presentation can be complicated by the presence of other entities particularly frequent in: autoimmune disorders (especially Sjogren syndrome) [91], monoclonal gammopathy of undetermined significance and lymphoproliferative disorders [92–94].

Since localised AL *per se* does not impact survival (patients survival is similar to general population) [4], treatment is only required for symptomatic disease. Treatment is generally proposed in more than 50–70% of patients and is effective in 50–80% of cases, depending on organ localisation [89]. Surgical removal of amyloidosis is the most frequent, direct and effective treatment when feasible. In laryngeal locAL, endoscopic surgery with laser CO_2 has been proven effective [95]. Radiotherapy has proven effective in small case series and may be considered in selected cases [96,97]. Systemic chemotherapy is not required in localised AL in general. Local progression with recurrence of the amyloidoma or with progression of amyloid deposition in adjacent anatomic sites can occur in 17–31% of cases [4,89,90,98]. Patients who responded to local treatment have a lower risk of progression and it has been hypothesised that local B-cell clone and the inflammatory infiltrate may play a role in progression [86,90].

Recommendation:

- *Local treatment (surgical, laser or cytotherapeutic debulking) (Grade B; Level III)*
- *Chemotherapy is not generally recommended*

Anti-amyloid fibril treatments

Monoclonal antibodies (MoAb) directed against the amyloid fibrils or serum amyloid P-component (SAP) have been developed. However, controlled trials of the anti-SAP MoAb (dezamizumab) plus the SAP-depleting agent (miridesap) and of the anti-fibril MoAb birtamimab were interrupted due to unfavourable risk-benefit profile [99] or futility [100]. Nevertheless, a signal of efficacy of birtamimab in patients at Mayo Clinic stage IV was seen and clinical trials are planned in this setting. The anti-amyloid light chain MoAb CAEL-101 that binds amyloid deposits *in vivo* gave promising results in early single-arm studies [101,102] and randomised trials in cardiac AL amyloidosis are underway (NCT04512235, NCT04504825).

The antibiotic doxycycline can inhibit amyloid fibril formation *in vivo* [103] and abrogate light chain toxicity [104]. A couple of small retrospective studies showed that doxycycline may reduce early mortality in cardiac patients when used as antibiotic prophylaxis along with effective chemotherapy [105,106], and a controlled study is underway (NCT03474458). A recent randomised study from China failed to show benefit of doxycycline added to standard of care [107]. At present, the use of amyloid-targeting agents cannot be recommended outside clinical trials.

Recommendation:

- *Doxycycline (Grade C; Level IV)*
- *Antifebrile antibodies are not recommended outside of clinical trials*

Conclusion

The treatment of AL amyloidosis has evolved with first treatment licenced in 2021. Despite this, majority of treatment recommendations are based on small phase II studies, retrospective studies and expert consensus. The recommendations suggested follow the grade classification for levels of evidence (Table 2). For all treatment options, the recommendations of this committee are to follow the clinical presentation which determines treatment tolerance tempered

Table 2. Levels of evidence.

Level of evidence	Grade of recommendation	Basis
Ia	A	Evidence obtained from meta-analysis of randomised controlled trials
Ib	A	Evidence obtained from at least one randomised controlled trial
IIa	B	Evidence obtained from at least one well-designed, non-randomised study, including phase II trials and case-control studies
IIb	B	Evidence obtained from at least one other type of well-designed, quasi-experimental study, i.e. studies without planned intervention, including observational studies
III	B	Evidence obtained from well-designed, non-experimental descriptive studies. Evidence obtained from meta-analysis or randomised controlled trials or phase II studies which is published only in abstract form
IV	C	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Table 3. Recommendations for non-transplant treatment of AL amyloidosis.

				Recommended treatments	
Status	Patient		Risk assessment	First choice	Alternative
Newly diagnosed	Patients without significant neuropathy		Cardiac stage I–IIIa	Dara-CyBorD[A]	CyBorD[B] VMDex[A]
			Cardiac stage IIIb	Dose modified Dara-CyBorD[C] Single agent daratumumab[C]	Dose modified CyBorD[B] Or VMDex[B]
	Patients with significant neuropathy		All stages*	Single agent daratumumab[C] Lenalidomide-Dexamethasone[B]	MelDex[B] Carfilzomib-Dex[C] Venetoclax[C]
Relapsed	Proteasome inhibitor Naïve or prolonged response to 1st line PI		All stages*	CyBorD/VMDex[B] Ixazomib-Dex[A]	Dara-V(C)D[C]
	Proteasome Inhibitor Exposed	Daratumumab Naïve	All stages*	Single agent daratumumab[B] Dara-V(C)D [C]	Dara-RD[B] Isatuximab[C]
		IMiD Naïve	All stages*	Lenalidomide-Dexamethasone (±cyclophosphamide)[B]	IRD[B]
		Lenalidomide refractory	All stages*	Pomalidomide-Dexamethasone[B]	Bendamustine[B]
		t(11;14)	All stages*	Venetoclax[C]	Venetoclax-Bortezomib-Dexamethasone[C] MelDex[C]
IgM related AL (With lymphoid component in the marrow)			All stages*	Rituximab-Bendamustine[C] ASCT [C]	Rituximab-bort-Dex[C] Rituximab-Cyclo-Dex[C] CyBorD[C] Ibrutinib (±Ritux)[C]

Dara: Daratumumab; CyBorD: cyclophosphamide-bortezomib-Dexamethasone; VMDex: bortezomib – melphalan-dexamethasone; VCD: bortezomib -cyclophosphamide-dexamethasone; VD: bortezomib -dexamethasone; Ritux: Rituximab; MelDex: oral melphalan dexamethasone; IRD: Ixazomib-lenalidomide-Dexamethasone; Dex: dexamethasone.
Stages: defined as per the European update of Mayo 2004 staging system.
*Dose modification and adjustments mandatory in patients with advanced end organ damage (cardiac or other).
[A,B,C]Levels of available evidence for the recommendation.

by potential side effects which limit use of drugs in AL (Table 3). All patients with AL amyloidosis should be considered for clinical trials where available. Targeted agents like venetoclax need urgent prospective evaluation. Treatment of the most unwell patients (those with advanced cardiac AL amyloidosis) remain unsatisfactory and poorly studied. Future prospective trials should include advanced stage patients with allow for evidence-based treatment decisions. Therapies targeting amyloid fibrils or those reducing the proteotoxicity of amyloidogenic light chains/oligomers are urgently needed.

Limitations

These guidelines are represented as opinions of the key and experienced leaders in the field of AL amyloidosis since there are not many randomised clinical trials or evidence-based data on this topic of this rare disease.

Disclaimer

The guidance may not be appropriate to all patients with AL amyloidosis and in all cases individual patient circumstances should be reviewed to decide a clinically appropriate approach including an alternative approach to the suggestions in the guideline. These recommendations should not be interpreted as setting a standard of care, or be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results.The ultimate judgement regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biological behaviour of the disease. These recommendations reflect the best available data at the time this document was prepared. The results of future studies may require revisions to the recommendations in this document to reflect new data.

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