Systemic Light Chain Amyloidosis

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81.1 Definition and Epidemiology

Systemic light chain (AL) amyloidosis is a protein misfolding and deposition disorder with an incidence of 5–12 persons per million per year. Clonal plasma cells or rarely B cells produce immunoglobulin light chains with the potential to misfold. These light chains are deposited as extracellular amyloid fibrils in peripheral tissues and cause morbidity and mortality. Organs most frequently involved are the kidney, heart, liver, autonomic and peripheral nervous system, gastrointestinal tract, and soft tissue.

81.2 Diagnosis

AL amyloidosis should be suspected in any patient with a monoclonal gammopathy and a compatible clinical syndrome such as heart failure with a preserved ejection fraction, nephrotic range proteinuria, unexplained weight loss, peripheral neuropathy, a bleeding diathesis, or carpal tunnel syndrome. Gammopathy work-up should include a serum-free light chain assay, immunofixation of serum and urine, bone marrow cytology, flow cytometry, histology and iFISH, and a full-body scan to exclude bone lesions due to symptomatic MM. AL amyloidosis is diagnosed by histopathology with Congo red staining and the typical apple-green birefringence under polarized light. Screening biopsies such as abdominal fat, rectum, salivary gland, or bone marrow as well as symptomatically involved organs can be utilized. The amyloid subtype has to be further confirmed by immunohistochemistry, immune electron microscopy, or laser microdissection and mass spectrometry.

81.3 Classification

AL amyloidosis can be classified by the origin of the underlying bone marrow disease: a clonal plasma cell or a lymphoid dyscrasia. Plasma cell dyscrasias can further be divided into monoclonal gammopathy, smoldering MM, and symptomatic MM. Finally, IgM-related AL amyloidosis is a specific entity with an underlying lymphocytic, lymphoplasmacytic, or a plasma cellular clone, commonly with cardiac and peripheral nervous system involvement.

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81.4 Risk Factors and Prognostic Scores

The underlying bone marrow disease as well as organ damage-related biomarkers can be utilized to stratify patients into risk groups. A bone marrow plasma cell infiltration above 10% (Hwa et al. 2016) and a high difference between involved and uninvolved serum-free light chain (dFLC) are negative prognostic factors (Kumar et al. 2012) for overall survival. Comparable to MM genetic aberrations can be detected on iFISH in plasma cell dyscrasias and be utilized to predict response to specific treatments (e.g., in patients with translocation (11;14) HDM/HSCT is more effective) (Bochtler et al. 2016).

The Mayo clinic first published a staging system utilizing NT-ProBNP and cardiac troponins (cTnI, cTnT) in 2004 which strongly predicted outcome. Median survival for patients in Stages I, II, and III were 26.4, 10.5., and 3.5 months (Dispenzieri et al. 2004a), and for the transplant group Stages I and II median were not reached, and Stage III median was 8.4 months (Dispenzieri et al. 2004b). This staging system was adapted in 2013 by a European cooperative approach and an ultra-high-risk patient group was identified with an NT-proBNP cut-off of 8500 ng/L (Stage IIIb) which must be considered transplant-ineligible (Wechalekar et al. 2013).

For patients with renal involvement, total proteinuria/24 h and estimated glomerular filtration rate (eGFR) can anticipate the risk for terminal renal failure (Palladini et al. 2014).

The depth of response is also a significant prognostic factor as patients achieving an amyloidosis VGPR (dFLC below 40 mg/L) or CR after treatment have a significantly better outcome (Palladini et al. 2012).

81.5 First-Line Treatment

Risk-adapted treatment is preferred since most patients are fragile and do not tolerate standard used dosing regimens (see Table 81.1). Three categories are defined with low-risk patients, transplant eligible, being a minority (≤20%). High-risk patients are defined by Stage IIIb and/or having NYHA class III or IV heart disease. Other factors to consider are age, performance status, eGFR, and systolic blood pressure (Palladini and Merlini 2016). Frequent assessments of hematological response during treatment are needed, and the goal is to achieve a CR or VGPR as a deep hematologic response is closely related to survival. Patients having a hematologic response may gradually achieve an organ response.

Table 81.1 First-line treatment options according to risk status

Risk status	Treatment
Low-risk Stage I	• (± induction treatment) MEL (200 mg/m^2) + auto-HSCT • CYBorD
Intermediate-risk Stages II–IIIa	• MEL-DEX • CYBorD • Bortezomib-MEL-DEX or LENA-MEL-DEX
High-risk Stage IIIb	• Low-dose therapies • Bortezomib weekly monotherapy

CYBorD cyclophosphamide, bortezomib, dexamathasoone

81.6 Second-Line Treatment

There is no randomized trial data to guide treatment at relapse. Patients with a good duration of response who tolerate initial treatment well may be retreated with the same initial regimen. Patients with a poor response are best treated with an alternative agent combination using agents to which the patient has not been exposed, palliation or in a clinical trial tailored to the individual patient in terms of their age, comorbidities, extent of organ involvement, and the patient's wishes. Lenalidomide and pomalidomide can be considered in relapsed disease although data on durability of response are limited (Dispenzieri et al. 2007; Palladini et al. 2017). Toxicity with lenalidomide is a significant issue, and it is recommended to start at a dose of 15 mg daily, with further dose reduction based on glomerular filtration rate (GFR) (Dispenzieri et al. 2007).

81.7 Autologous HSCT

81.7.1 Indication

Eligibility criteria for autologous HSCT are variable depending on the transplanting center. However, the usual eligibility criteria include age ≤70 years, performance status 0–2, NYHA class I or II, absence of significant clinical cardiac involvement (NT pro BNP <5000 ng/L. left ejection fraction ≥45 to 50%), absence of severe orthostatic hypotension (i.e., systolic blood pressure ≥90 mm Hg), and eGFR >40 mL/min. Induction therapy before stem cell mobilization can be given, especially in patients who fulfill (smoldering) myeloma definition criteria, i.e., ≥10% bone marrow plasma cell infiltration.

The correct selection of patients is extremely important since the mortality associated with autologous HCT in AL amyloidosis can be unacceptable high if not done properly. Since the selection criteria also include the cardiac biomarkers, treatment-related mortality has dropped from around 20% to 5%; also see Table 81.2 (Gertz et al. 2013).

81.7.2 Recommended

Stem cell mobilization and leucapheresis can be associated with unusual morbidity, and a syndrome of hypoxia and hypotension has been described both during mobilization with G-CSF and during the leucapheresis procedure itself, probably as a result of a capillary leak syndrome triggered by G-CSF. Therefore, use of reduced doses of G-CSF (such as 10 μg/kg per day for 4–5 days) is recommended. In low-burden disease (i.e., plasma cells <10%), the use of CY mobilization chemotherapy does not seem to be necessary.

Conditioning regimens are based on high-dose MEL. The usual MEL dose is 200 mg/m^2, since lower-dose melphalan is associated with decreased hematological response and PFS and therefore other treatment non-transplant options may be more suitable (Cibeira et al. 2011).

81.7.3 Results

Figure 81.1 shows OS of auto-HSCT until 2010. In Table 81.2 the more recent publications of the last 10 years have been summarized. The use of induction therapy before HSCT has been more frequently applied and seems to demonstrate better hematologic responses than HSCT alone.

81.8 Allogeneic HCT

The largest retrospective analysis on allo-HCT for AL amyloidosis was performed by the EBMT in 2006 (Schönland et al. 2006). Nineteen patients were analyzed. Seven patients received MAC, and eight RIC. 40% of patients died of TRM. Long-term survival and sustained CR were achieved in seven patients and were associated with chronic GVHD in the majority of them. DLI has been successfully performed in a few patients with AL amyloidosis, thereby demonstrating a potent "graft-versus-plasma cell-dyscrasia" effect.

The EBMT initiated a noninterventional prospective study (NIS) for patients with AL amyloidosis undergoing allo-HSCT. Preliminary results have been presented in 2016 with improved overall survival (see Fig. 81.2). Allo-HSCT after RIC can be discussed as a treatment option for relapse after auto-HCT in patients <60 years with preserved organ functions and a HLA-identical donor. It might be a curative treatment for highly selected patients.

Table 81.2 Summary of the outcome of patients with systemic AL amyloidosis undergoing autologous stem cell transplantation, according to the more recent publications

Source	Type	No. of patients	Overall response rate (CR) %	TRM (%)	Overall survival (%)
Landau et al. (2017)	Retrospective	143	CR 43% at 12 months (83 pts only)	5%	Median 10.4 years
Sanchorawala et al. (2015)	Prospective bortezomib-DEX induction	35	ORR 100% CR 63%	8.5%	5 years; 83%
Hazenberg et al. (2015)	Prospective VCR-adriam-DEX induction	69	ORR 46% CR 13%	4%	Median 10 years
Parmar et al. (2014)	Retrospective	80	ORR 75% CR 18.6%	7.5%	10 years, 56%
Huang et al. (2014)	Prospective bortezomib-DEX induction in 28 pts	56	ORR 85.7% and 53.5% CR 67.9% and 35.7% Both at 12 months	3.6%	2 years 95% and 69.4%
D'Souza et al. (2015)	Retrospective	1536	ORR 71% CR 37% (2007–2012 cohort)	5% (2007–2012 cohort)	5 years 77% (2007–2012 cohort)
Cibeira et al. (2011)	Retrospective	421	CR 34%	5.6% (2004–2008 cohort)	Median 6.3 years

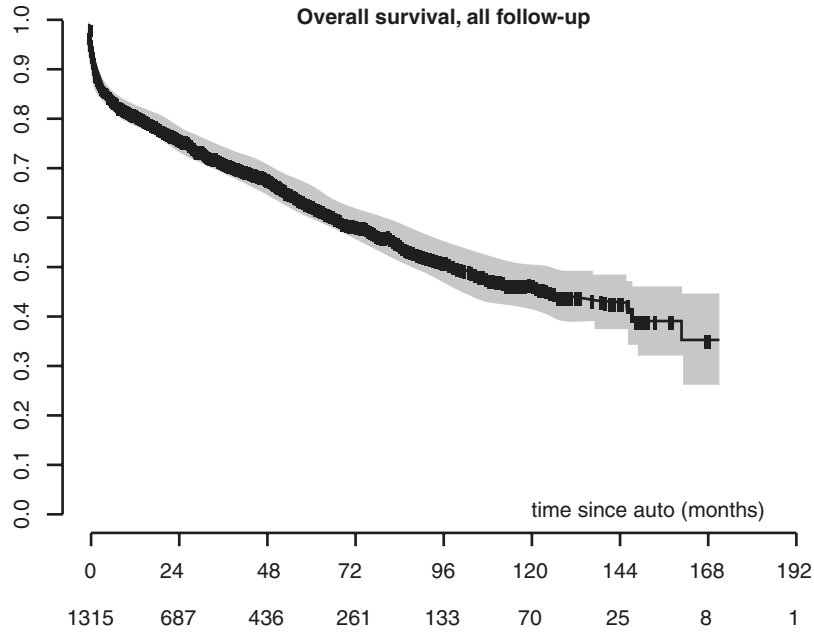

Fig. 81.1 Autologous EBMT data (patients treated until 2010)

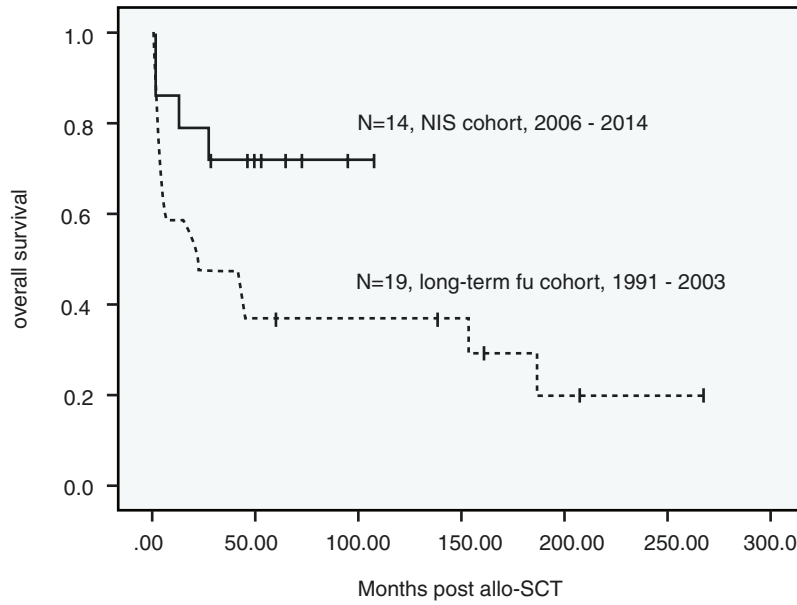

Fig. 81.2 Long-term overall survival after allo-HSCT, an EBMT analysis of patients with AL amyloidosis

Key Points

- AL amyloid therapy is directed against the underlying B cell clone
- Hematological response is the goal of therapy and improves survival
- Intensity of chemotherapy has to be risk adapted
- High-dose chemotherapy with auto-HSCT is the therapy of choice for low-risk patients
- Allo-HSCT might be a curative treatment option for relapse after auto-HCT in younger patients with preserved organ functions and a HLA-identical donor

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