Update on treatment of light chain amyloidosis

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ABSTRACT

Light chain amyloidosis is the most common type of amyloidosis as a consequence of protein misfolding of aggregates composed of amyloid fibrils. The clinical features are dependent on the organs involved, typically cardiac, renal, hepatic, peripheral and autonomic neuropathy and soft tissue. A tissue biopsy or fat aspirate is needed to confirm the presence/type of amyloid and prognostic tools are important in a risk stratified approach to treatment. Autologous stem cell transplant eligibility should be assessed at baseline, weighing the reversible or non-reversible contraindications, toxicity of treatment and chemotherapy alternatives available. Chemotherapy options include melphalan, thalidomide, bortezomib, lenalidomide, bendamustine in combination with dexamethasone. Many studies have explored these treatment modalities, with ongoing debate about the optimal first line and sequential treatment thereafter. Attaining a very good partial response or better is the treatment goal coupled with early assessment central to optimizing treatment. One major challenge remains increasing the awareness of this disease, frequently diagnosed late as the presenting symptoms mimic many other medical conditions. This review focuses on the treatments for light chain amyloidosis, how these treatments have evolved over the years, improved patient risk stratification, toxicities encountered and future directions.

Introduction

Amyloidosis is a rare systemic disorder characterized by misfolding of aberrant precursor proteins causing formation of unstable auto aggregates leading to amyloid fibril formation in a predominant β-pleated sheet structure.[1] These fibrils are deposited in different organs, progressively affecting the organ's architecture and function.[2] The unstable protein may be hereditary or acquired. The most common organs involved include the heart, kidneys, liver, gastrointestinal tract, autonomic and peripheral nervous system. Systemic light chain (AL) amyloidosis is the most common type: in which the amyloidogenic protein is a monoclonal light chain secreted by an underlying clonal plasma cell (or rarely B lymphoid) dyscrasia.[2]

Amyloidosis caused by deposition of misfolded transthyretin (TTR) is the next most common, either hereditary (due to amyloidogenic TTR mutations) or a disease of aging due to wild-type TTR deposition (senile systemic amyloidosis). Other hereditary amyloidoses are due to amyloidogenic mutations in fibrinogen, Apolipoprotein A1 and A2, lysozyme and gelsolin genes. AA amyloidosis occurs due to deposition of serum amyloid A protein (an acute phase protein) in a spectrum of disorders causing prolonged inflammation, and treatment focuses upon reducing that inflammatory drive. Table 1 illustrates the common types of systemic amyloidosis.[3] Localized AL amyloidosis is characterized by amyloid deposits at a single site (commonly in bladder, skin, larynx, lung) due to local production of light chains and no evidence of systemic involvement. It has excellent prognosis with generally no need for systemic therapy.[4] This article focuses upon recent advances in treatment of systemic AL amyloidosis.

Clinical presentation and diagnosis

The presenting symptoms of AL amyloidosis have a wide spectrum: dyspnea, lethargy, weight loss, bleeding tendency, swelling of lower limbs, frothy urine, orthostatic hypotension or peripheral neuropathy. Macroglossia and peri-orbital bruising are almost pathognomonic, occurring only in a third of all cases (Figure 1). The diagnosis of AL amyloidosis is often delayed as presenting features are subtle or mimic other more common conditions.

Advanced organ dysfunction has often ensued prior to a clinical diagnosis of amyloidosis although monoclonal gammopathy (MGUS)[5] or myeloma usually pre-dates a diagnosis of amyloidosis. Fifteen percent of patients with myeloma have symptomatic AL amyloidosis and up to 30% may have 'incidental' deposits, which may become clinically significant with improving long-term outcomes in myeloma.[6] Patients with MGUS and an abnormally elevated free light chain (FLC) should be additionally monitored at each visit by measurement of serum brain natriuretic peptide (BNP or its N-terminal fragment, NT-proBNP) and urine for albuminuria; abnormal presence of either may herald development of amyloidosis[1] before advanced, symptomatic organ damage, thus significantly reducing the early deaths which are still observed.

Confirmation of diagnosis needs demonstration of amyloid deposition; pathognomonic apple green birefringence by Congo red staining using crossed polarized light on histological tissue sections of either the affected organ, bone marrow,

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rectum or abdominal fat aspirate (the latter being an easy bedside procedure available for all patients including those with hemostatic impairment).[7] Fibril typing is critical in deciding appropriate therapy and performed by immunohistochemistry (widely available but specific only in 75-80% of cases of AL),[8] immunoelectron microscopy (highly specific but limited availability),[9] or lately, mass spectrometry of amyloid deposits obtained by laser capture (rapidly becoming an invaluable adjunct)[10] (Figure 2). Detecting the underlying clone requires serum and urine electrophoresis and immunofixation, serum free light chain analysis, bone marrow examination and imaging for presence of myeloma-related bone disease.

Base-line assessment of organ function (Table 2) is

Table 1. Common types of systemic amyloidosis.

Type	Abbreviation	Precursor protein	Site of synthesis	Clinical symptoms (in order of frequency of organ involvement)	Specific Treatment
Immunoglobulin light chain amyloidosis	AL	Monoclonal Light Chain	Bone marrow plasma cells or B-cell clone	Renal, cardiac, PNS/ANS, GI, soft tissue	Chemotherapy, ASCT, organ transplant
Senile systemic amyloidosis	SSA (ATTR – wild Type)	Wild type transthyretin	Liver	Cardiac, carpal tunnel syndrome	Supportive (optimal CHF control), Doxycycline*, Diflunisal*
Hereditary transthyretin amyloidosis	ATTR - mutation	Greater than 100 variant mutations	Liver	PNS/ANS, cardiac, vitreous involvement, leptomeninges	Liver transplantation (V30M mutation), supportive (cardiac and symptomatic PNS/ANS) Diflunisal*, Tafamidis*
Systemic AA	SAA	Serum amyloid A	Liver	Renal, GI, liver	Suppression of Inflammatory disorder Eprodisate*
Fibrinogen amyloidosis	Afib	Fibrinogen α chain	Liver	Renal, liver	Renal replacement therapy, renal (&/or liver) transplant
Apolipoprotein A1 A1	AApoA1	Apolipoprotein	Liver, intestine	Renal, liver, cardiac, larynx	Organ transplantation Supportive

AL: light chain amyloidosis; SSA: senile systemic amyloidosis; ATTR: amyloidogenic transthyretin mutations; SAA: systemic amyloidosis A; Afib: fibrinogen amyloidosis; AApoA1: Apolipoprotein A1; PNS: peripheral nervous system; ANS: autonomic nervous system; GI: gastro-intestinal; ASCT: autologous stem cell transplant; CHF: congestive heart failure denotes treatments currently in clinical trials.*

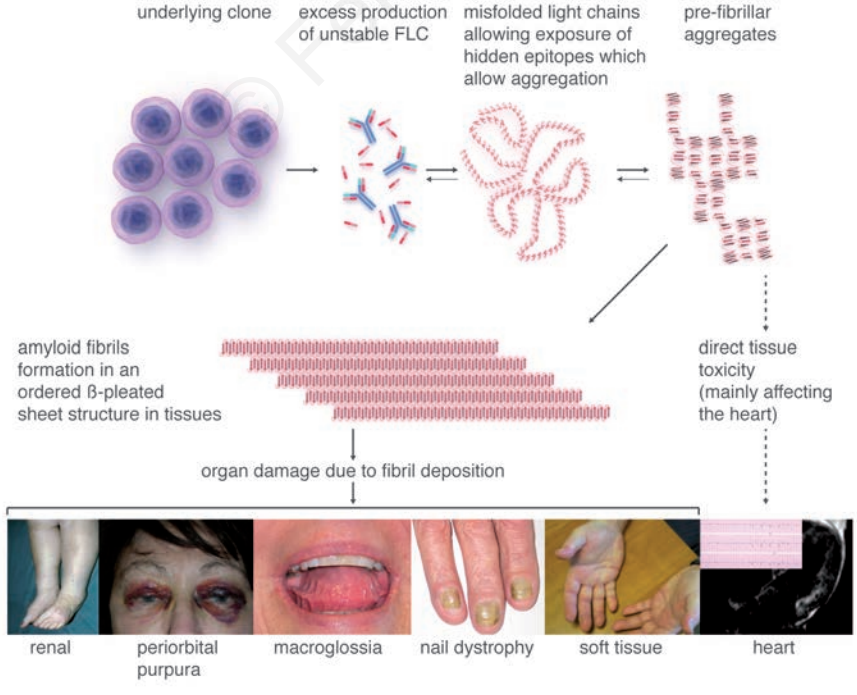


Figure 1. Pathogenesis and presentation of AL amyloidosis. Direct deposition of amyloid fibrils lead to the typical clinical features depicted: periorbital bruising; macroglossia with indentation of teeth marks of the tongue; nail dystrophy; lower limb edema with nephrotic syndrome; soft tissue infiltration of hands bilaterally; ECG showing small QRS complexes and late gadolinium enhancement of cardiac MRI. The pre-fibrillar light chain aggregates (and possibly the misfolded light chains) can have direct tissue toxicity. Cardiac toxicity of light chains appears to be a significant contributor to myocardial dysfunction seen in AL amyloidosis. This may also be the reason for rapid improvement in NT-proBNP which parallels a hematologic response to therapy often without any evidence of structural cardiac improvement but correlating with clinical improvement in the patients' cardiac symptoms.

important for prognosis and selection of therapy. Formal testing for autonomic and peripheral neuropathy may be needed in selected cases. ^{123}I labeled serum amyloid P component (SAP) scintigraphy (if available), is useful for diagnosis, quantification and especially valuable in serial monitoring of amyloid deposits (Figure 3).[11] Cardiac magnetic resonance imaging (CMR) is more sensitive and specific than echocardiography for diagnosis of cardiac amyloidosis, showing a characteristic subendocardial late gadolinium enhancement. A cardiac biopsy may be needed in a select cohort of patients with isolated cardiac amyloidosis and MGUS to differentiate AL amyloidosis from senile systemic amyloidosis/ATTR amyloidosis due to V122I mutation. Bone scintigraphy tracers, ^{99}mTc-dicarboxypropane diphosphonate (^{99}mTc-DPD) and ^{99}mTc-pyrophosphate (^{99}mTc-PYP) are avidly taken up in cardiac ATTR amyloid deposits but not in AL;[12,13] this represents an emerging non-invasive means of differentiating the two conditions (Figure 3).

Risk stratification is an essential part of the diagnostic workup and cardiac involvement determines the risk. The Mayo Clinic group, using NT-proBNP and troponin T or I (or more recently, using high sensitivity troponin[14] and more recently serum free light chains),[15] defined stages in AL amyloidosis depending on none, one or both being greater than the threshold levels (median survival of 26.4, 10.5 and 3.5 months, respectively);[16] even with newer therapies, Mayo stage III disease still has a poor median survival of seven months.[16] NT-proBNP over 8500 ng/L and systolic blood pressure below 100mmHg identify a subgroup of stage III patients with a very high risk of early death.[16] Confounding factors, like renal failure, impact the concentration of NT-proBNP, and measurement of BNP may be preferred in this setting.[17]

Table 2. Diagnostic and Staging Investigations for systemic AL amyloidosis.

Tissue diagnosis	Abdominal fat aspirate Salivary gland or rectal biopsy Biopsy of involved organ
Amyloid typing	Immunohistochemistry (immuno-electron microscopy if available) Mass spectometry DNA analysis (if indicated)
Studies to detect an underlying plasma/B-cell clone	Serum and urine electrophoresis and immunofixation Serum free light chain measurement Bone marrow aspirate / biopsy (plus FISH) Imaging studies for bone disease
Assessing of organ involvement and staging	**Cardiac** NT-proBNP (or BNP), cTnT (or hs-cTnT, or cTnI) Echocardiography (plus strain imaging) ECG (plus Holter ECG) Cardiac MRI (if indicated) ^{99}mTc-DPD scan (if indicated) **Renal** 24 h urinary protein Serum creatinine (and eGFR) Liver Liver function tests Liver US / CT scan **Nerves** Nerve conduction studies (if indicated) Autonomic testing **Whole body amyloid load** ^{123}I labeled SAP scintigraphy (if available)

FISH: fluorescent in situ hybridization; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; BNP: brain natriuretic peptide; cTnT or cTnI: troponin T or I; hs-cTnt : high sensitivity troponin T; ECG: electrocardiograph; ^{99}mTc-DPD scan: ^{99}mTc-dicarboxypropane diphosphonate scan; eGFR: estimated glomerular filtration rate; US: ultrasound; CT: computed tomography; MRI: magnetic resonance imaging; SAP: serum amyloid P.

Treatment of AL amyloidosis

Goals of therapy

The aim of treatment in AL amyloidosis is eradicating the fibril precursor protein by suppressing production of free light chains as rapidly as possible by targeting the underlying clonal plasma/B cell dyscrasia, whilst minimizing treatment-related mortality (TRM) and morbidity[1] with supportive measures to preserve organ function. Since patients with AL amyloidosis have a small clonal burden[18] and lack the high-risk cytogenetic features seen in myeloma such as t(4:14) or del17p,[19] shorter courses of dose-adapted chemotherapy may be adequate to achieve good hematologic responses.[20]

Response assessment has two components: hematologic and organ response, and the latter follows the former.[21,22] dFLC measurement is a key marker to assess clonal disease response.[22] Consensus criteria for hematologic response assessment have recently been published (Table 3).[23] A very good partial response (VGPR) (defined as dFLC less than 40 mg/L) or better is associated with an OS of 80-90% at three years,[23] and is currently considered the minimum goal of therapy.

In addition to standard measures of organ function, cardiac biomarkers such as a reduction in NT-proBNP of 30% and 300 ng/L from baseline following completion of therapy usefully define a cardiac organ response.[22] Lack of such a decrease in NT-proBNP (in patients with heart involvement) identifies a subgroup of patients achieving less than CR who need a more profound hematologic response. Factors such as worsening renal failure or treatment with immunomodulatory drugs may lead to elevated cardiac biomarkers, confounding response assessment.[24]

Supportive care

Supportive treatment, aimed at improving or palliating organ function, maintaining quality of life, and prolonging

Table 3. Consensus hematologic response in systemic light chain (AL) amyloidosis.[22]

Hematologic Response	Criteria
Complete Response (CR)	Normal serum free light chain ratio with negative serum and urinary immunofixation
Very good partial response (VGPR)	The difference in the free light chains (dFLC) less than 40mg/L
Partial Response (PR)	A reduction in the dFLC greater than 50%
No response	A less than 50% response in dFLC

CR: complete response; VGPR: very good partial response; PR: partial response; dFLC: difference between involved and uninvolved free light chains.

survival while anti-plasma cell therapy has time to take effect, has an important impact upon survival and is a fundamental part of an integrated treatment. It requires the co-ordinated expertise of several specialists familiar with the disease. Patient education with daily weight, judicious diuretic use, low salt diet, salt-poor albumin, cautious angiotensin converting enzyme-inhibitors, use of thigh-high stockings, midodrine for postural hypotension and close multidisciplinary monitoring make lifesaving differences. Diarrhea, malabsorption and malnutrition may be ameliorated by antimicrobial therapy for bacterial overgrowth, reduced gut motility with opioids (codeine phosphate and loperamide) with addition of octreotide in non-responsive cases, prokinetic agents for gastroparesis, percutaneous endoscopic gastrostomy (PEG) feeding in those with marked macroglossia impairing swallowing or parental feeding in malabsorption. Amiodarone may have a role in cardiac arrthymias, a common cause of death in AL. Implantable cardioverter defibrillators (ICD) are increasing considered in patients with life-threatening ventricular arrhythmias, but there is no definite evidence of survival advantage at present.[13]

Autologous stem cell transplantation

High-dose melphalan and autologous peripheral blood stem cell transplantation (ASCT) has been routinely used as treatment for AL amyloidosis since the first reports in the mid-1990s at Boston University[25,26] (Table 4). Contrary to the common experience with ASCT in multiple myeloma, the toxicity of the procedure can be higher in AL, e.g. a 15% incidence of major complications during stem cell mobilization and collection, and mortality 2-10%[50] in patients with cardiac or multi-organ involvement. Over the last decade, complications of ASCT in AL patients have been well appreciated and addressed; appropriate patient selection is the key to reduction in morbidity and mortality. A small French randomized controlled trial failed to show a difference in survival with ASCT over conventional chemotherapy with oral melphalan and dexamethasone, with similar clonal hematologic response

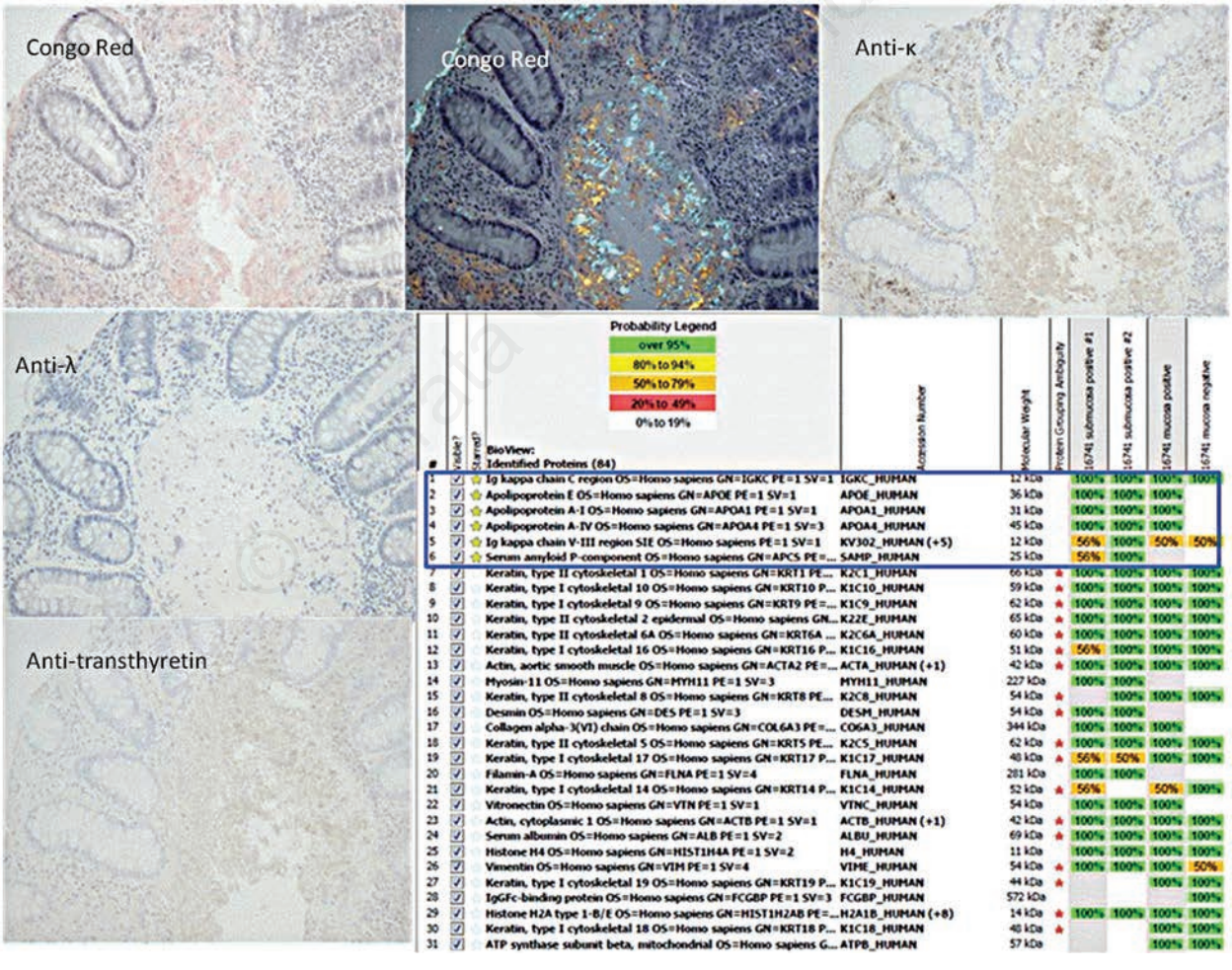
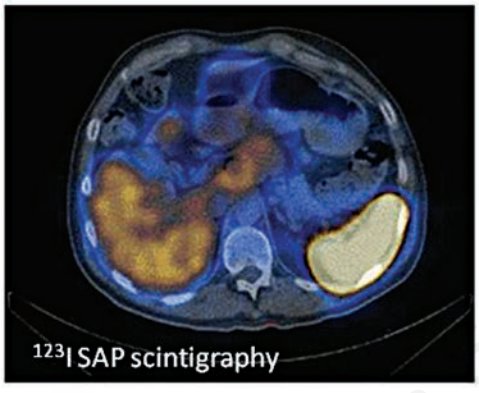


Figure 2. Confirming the diagnosis and fibril typing in a patient with AL amyloidosis due to underlying kappa light chain secreting plasma cell dyscrasia. Congo red staining demonstrates characteristic staining and apple green birefringence under cross polarized light. Immunostaining with antibodies to kappa light chains is positive and there is no staining with antibodies to lambda or transthyretin (or SAA (not shown) Proteomic analysis of the amyloidotic tissue shows presence of kappa light chains in addition to other proteins known to be present in amyloid fibrils (blue box). Also note the presence of keratin which is a common contaminant from the operator's skin showing the need for meticulous specimen preparation to avoid false positive results.

rates; 67% *versus* 68%, respectively,[30] but major limitations included high TRM of 24% in the ASCT arm and small sample size.[51] Dose-adapted melphalan strategy, with dose reduction to 100, 140 and 200 mg/m^2 depending on renal, cardiac parameters and age, increases a potentially suitable patient population, with lower doses potentially offering a reduced toxicity, but also reduced hematologic responses.[52]

The largest transplant experience in AL amyloidosis comes from the Mayo Clinic and Boston University. At Boston University, assessment by a multi-disciplinary team and use of risk stratification is employed to select patients for ASCT. Eligibility criteria include histological proof of amyloidosis, clonal plasma cell dyscrasia, age over 18 years, performance status (PS) 0-2 (Southwest Oncology Group or Zubrod), left ventricular ejection fraction over 40%, oxygen saturations over 95% on air and supine BP over 90 mmHg.1 Of 421 consecutive patients treated with ASCT in this center from July 1994 to December 2008, 55% received 200 mg/m^2 high-dose melphalan and 45% received modified dose melphalan (100-140 mg/m^2). On an intention-to-treat basis, 34% achieved a hematologic CR with an overall survival (OS) of 6.3 years. Of 340 evaluable patients, 43% achieved a com-



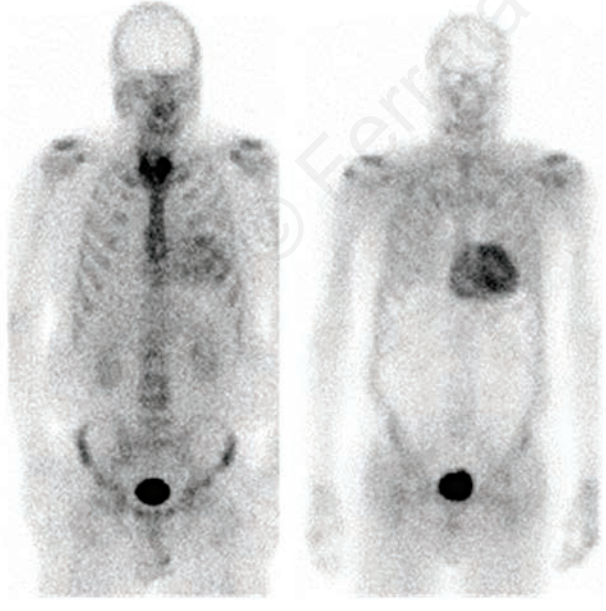
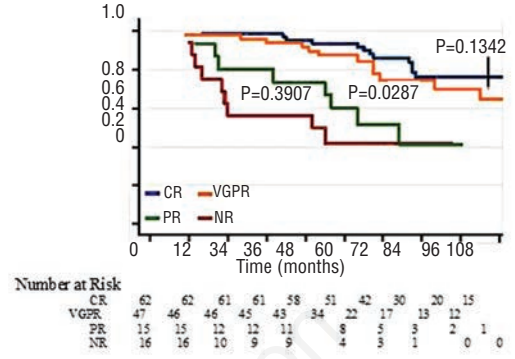
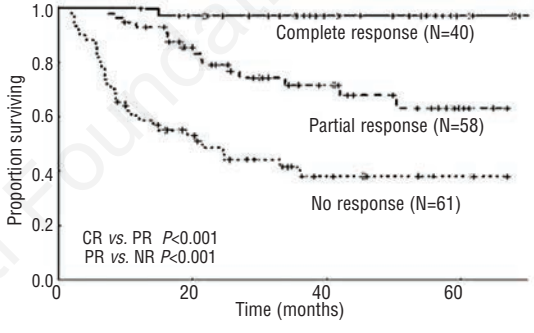


Figure 3. Radionuclide imaging in amyloidosis: ^{123}I labeled serum amyloid P component scintigraphy showing uptake in the spleen and liver in a patient with AL amyloidosis (left). The middle panel shows low-grade cardiac uptake of ^{99}mTc-DPD in a patient with AL amyloidosis compared with marked cardiac uptake of ^{99}mTc-DPD in a patient with wild-type transthyretin (senile cardiac) amyloidosis (right panel).





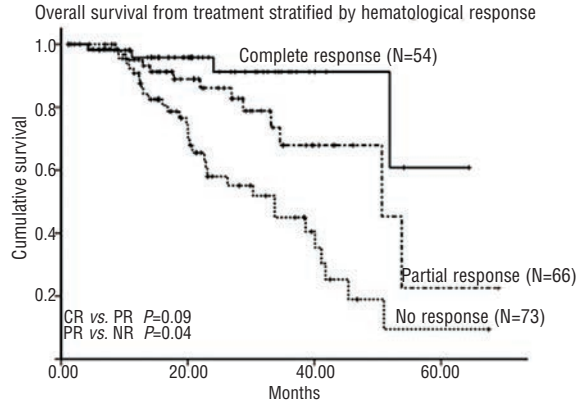


Figure 4. Overall survival in AL amyloidosis stratified by hematologic response in patients treated with high-dose melphalan and autologous stem cell transplantation in a landmark analysis of 140 patients showing superior OS in those achieving a CR and vGPR (median OS not reached; no significant difference between the groups *P*=0.13) *versus* those achieving a PR and NR (median OS 77 and 50 months respectively; with no significant difference; *P*=0.39).[53] (A) Oral melphalan dexamethasone[54] (B) Dose adapted cyclophosphamide-thalidomide-dexamethasone in 202 patients with the median OS 42 months; not reached at 60 months in patients achieving a CR; 50 months and 33 months for those achieving a PR and non-responders respectively.[55] (C) The survival is best in patients who achieve complete or very good partial response with either treatment modality. Note: these survival curves describe different cohorts of patients with varying selection criteria and are not directly comparable to each other. NR: no response; PR: partial response; VGPR: very good partial response; CR: complete response; dFLC; difference in involved and uninvolved free light chains.

plete response (CR) and 78% achieved organ responses. Comparison of those achieving a CR *versus* less than CR, the median event-free survivals (EFS) and OS were 8.3 and 13.2 years in the former and 2 and 5.9 years in the latter group, respectively. The overall TRM was 11.4%, with 5.6% in the latter five years, suggesting further refinement to patient selection with added investigations and staging criteria lowered the TRM.[1] A landmark analysis at one year in 140 patients with evaluable FLC results showed a superior OS in those achieving a CR and very good partial response (vGPR) *versus* those achieving a partial response (PR) and no response (NR) (Figure 4A).[53] The Mayo Clinic reported a series of 422 patients receiving an ASCT from March 1996 to December 2009. Transplant eligibility included age under 70 years, PS 0-2, troponin T below 0.06 ng/mL, creatinine clearance over 30 mls/min (unless on dialysis), New York Heart Association class I-II, and less than 2 organ involvement. The focus of this analysis was to examine the TRM before and after January 2006, with TRM pre-2006 as 12% and 7% post-2006.[56] Troponin T over 0.06 ng/L and NT pro-BNP over 5000 pg/ml were associated with a high TRM, whilst patients with both markers below the thresholds had a TRM of 1%.[57] Refining patient selection has allowed ASCT to be performed safely, but eligibility of patients for ASCT has decreased outside of centers with extensive transplant experience.

First major organ responses in AL were initially reported after ASCT in 2001; 36% of patients achieved a renal response at 12 months defined by the amyloidosis consensus criteria[1,50,52,53] proving that clonal responses in AL translate into organ responses. The depth of hematologic

Table 4. Chemotherapy regimens and ASCT studies in AL amyloidosis.

Chemotherapy / Reference	Number of patients	Hematologic response % (CR %)	Overall survival (months) or 1-3 year OS (%)
		Conventional chemotherapy	
Dex (Dhodapkar *et al.*)[27]	93	53 (24)	31
Cyclo/Thal/Dex (Wechalekar *et al.*)[20]	75	74 (21)	41
MDex (Palladini *et al.*)[28,29]	46	67 (33)	61
MDex (Jaccard *et al.*)[30]	68 (47)	56.9	
		Bortezomib containing regimens	
Bortezomib (Reece *et al.*)[31]	70	OW: 68.8 (37.5) TW: 66.7 (24.2)	OW: 94% (1 yr OS) TW: 84% (1 yr OS)
Bor/Dex (Kastritis *et al.*)[32]	94	71 (25)	76% (1 yr OS)
Cyclo/Bor/Dex (Venner *et al.*)[33]	43	81.4 (41.9)	97.7% (2 yr OS)
Cyclo/Bor/Dex (Mikhael *et al.*)[34]	17	94 (71%)	Not specified
Bor/Mel/Dex – 33	50	67 (27) stage I & II	Not reached
Cyclo/Bor/Dex -17		40 (5) stage III	58%
(Palladini *et al.*)[35]			(1 yr OS projected)
		Lenalidomide containing regimens	
Len/Dex (Sanchorawala *et al.*)[36]	34	67 (29)	Not specified
Len/Dex (Dispenzieri *et al.*)[37]	23	41	Not specified
Cyclo/Len/Dex (Palladini *et al.*)[38]	21	62 (5)	36
Cyclo/Len/Dex (Kastritis *et al.*)[24]	37	55 (8)	41% (2 yr OS)
Cyclo/Len/Dex (Kumar *et al.*)[39]	35	60 (11)	37.8
Mel/Len/Dex (Moreau *et al.*)[40]	26	58	80.8% (2 yr OS)
Mel/Len/Dex (Dinner *et al.*)[41]	25	58 (8)	58% (1yr OS)
Mel/Len/Dex (Sanchorawala *et al.*)[42]	16	50 (7)	Not reached
		Other regimens	
Bendamustine/Pred (Palladini *et al.*)[43]	36	47 (3)	65% (3 yr OS)
Pomalidomide/Dex (Dispenzieri *et al.*)[44]	33	48 (3)	76% (1 yr OS)
		ASCT	
ASCT (Jaccard *et al.*)[30]	50	67 (61)	22.2
ASCT (Vesole *et al.*)[45]	107	16 (1 yr)	56% (3 yr OS) 30 day TRM 18%
ASCT (Cibeira *et al.*)[1]	421	34% CR	75.6 100 day TRM 11.4%
ASCT (Goodman *et al.*)[46]	92	58% CR	63.6 100 day TRM 23%
ASCT (Venner *et al.*)[47]	88	28% CR	Not reached 100 day TRM 6.8%
ASCT & Thal/Dex consolidation	45 total	21% CR	84% (2 yr OS)
(Cohen *et al.*)[48]	31 TD	39% CR (1 yr)	TRM 4.4%
ASCT & Vel/Dex consolidation	40 total	27% CR	82% (2 yr OS)
(Landau et al.)[49]	23 VD	58% CR (1 yr)	100 day TRM 10%

Mel: melphalan; Pred, prednisolone; Dex: dexamethasone; Cyclo: cyclophosphamide; Bor: bortezomib; Thal: thalidomide; Len: lenalidomide; ASCT: autologous stem cell transplantation; TD: thalidomide and dexamethasone consolidation; VD: velcade and dexamethasone consolidation; OS: overall survival; yr: year; CR: complete remission; PR: partial remission; OW: once weekly; TW: twice weekly; TRM: transplant-related mortality.

response strikingly correlated with renal responses. Seventy-one percent of patients in CR had renal responses compared to 11% with persistence of the plasma cell dyscrasia. Over the last decade, improvements in quality of life, hepatic and cardiac responses have been published. Similar to renal responses, clinical responses in other organ systems are more evident with deeper hematologic responses. Organ responses can take up to 6-12 months or longer to occur. Hematologic CR occurs in just under half of all patients undergoing ASCT; strategies to improve hematologic CR rates following ASCT are an important focus. These include induction therapy prior to ASCT, novel conditioning and consolidation therapy. A current phase II trial to evaluate the role of induction treatment prior to ASCT using Bortezomib/Dexamethasone (Dex) is ongoing at Boston. Among the first 22 patients treated, according to intention-to-treat analysis, hematologic responses occurred in 79% (53% CR and 26% VGPR) of patients (for evaluable patients 67% CR).[58] Tandem cycles of HDM have been shown to improve the proportion of patients who ultimately achieve a hematologic CR, leading to an overall CR rate of 67%.[59] A pilot study incorporating bortezomib with high-dose melphalan (HDM) has shown promising results with high hematologic response rates.[58] Consolidation with thalidomide and dexamethasone is too toxic for routine use[48] but bortezomib and dexamethasone as consolidation give high and durable response rates including CR in 58% at 12 months,[49] with larger studies needed.

Combination chemotherapy

Alkylators and steroid-based regimens

Alkylating agents have formed the backbone of treatment of AL for over 40 years with melphalan and cyclophosphamide used in many current therapies. The first randomized controlled trials proved the efficacy of melphalan and prednisone[60] in this disease, but novel treatment options make this regimen less attractive given the few and slow hematologic responses, poor survival of 18 months and rarer organ responses.[60] Similarly, high-dose single agent dexamethasone[27] and vincristine, adriamycin and dexamethasone (VAD),[61] although effective, have been superseded due to toxicity and ease of administration, respectively, with recent regimens.

Melphalan-dexamethasone (MDex) regimen, pioneered by the Italian amyloidosis group, is well tolerated and

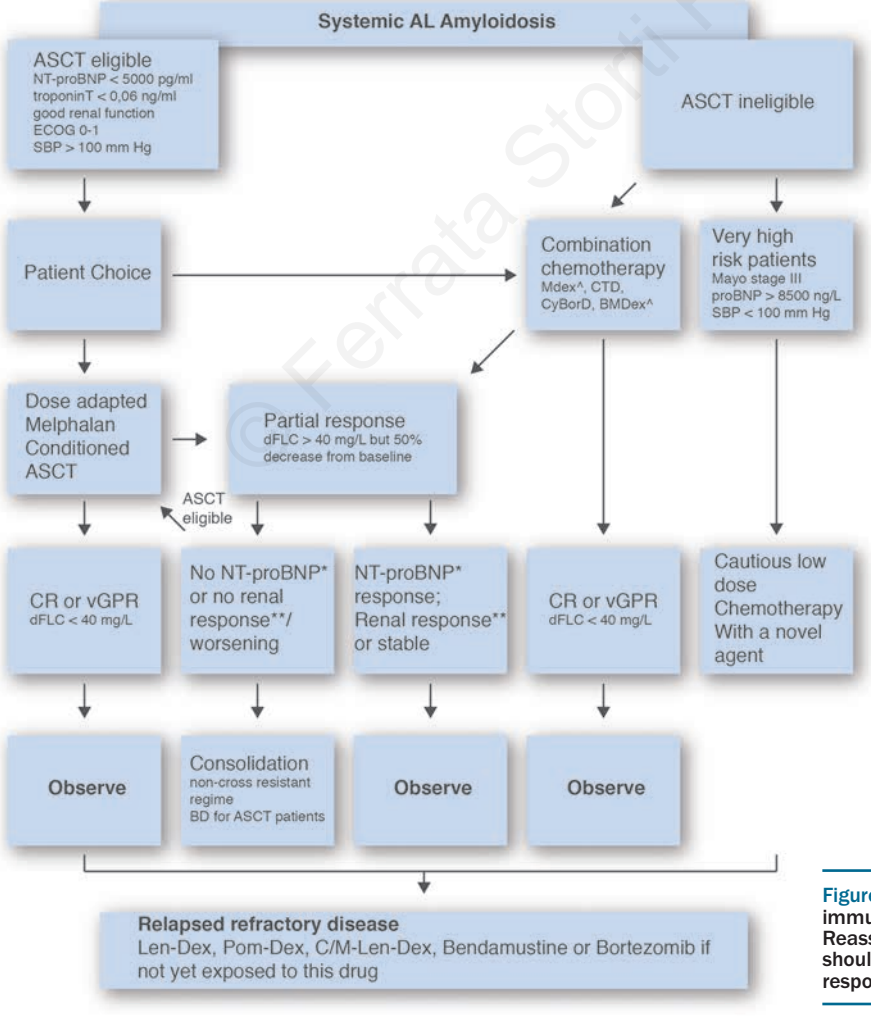


Figure 5. Therapy algorithm for treatment for immunoglobulin light chain (AL) amyloidosis. Reassessment post 3 cycles of chemotherapy should be undertaken to optimize hematologic response according to consensus criteria.[22]

associated with good hematologic and organ response rates of 67% and 33%, respectively, a third of patients achieving a complete clonal response. The median PFS and OS are 3.8 and 5.1 years, respectively;[28] results confirmed prospectively in subsequent studies (Figure 4B).[30,54] This regimen is usually well tolerated, with 10-15% experiencing severe adverse events, mainly fluid retention and cytopenias. Oral MDex is generally considered the standard of care for patients outside of clinical trials in a number of countries. However, the role of MDex in patients with advanced cardiac disease is uncertain. These patients have a median survival of 10.5 months[62] and lower response rates (11% CR and 33% PR in 61 patients with cardiac AL); another study reported a median survival of 17 months and 28% mortality in the first three months in patients treated with this regime.[63] But high early mortality makes this group difficult to treat regardless of the regimen. Intravenous intermediate dose melphalan (25 mg/m^2) had a 12% treatment-related mortality (TRM) in a UK study with prolonged remission in the responders,[64] but a recent prospective trial found this too toxic for routine use.[65]

Reduced toxicity of low-dose dexamethasone containing regimens in myeloma[66] make these appealing in AL amyloidosis. Melphalan and once weekly dexamethasone was associated with lower responses[67] than standard MDex[28] raising doubts as to this approach in AL where rapid and deep responses are desirable.

Bendamustine, an alkylator with a novel mechanism of action, with prednisone is useful in relapsed/refractory disease and achieved hematologic responses in 47% (n=17) with a survival advantage in responders in a 3-month landmark analysis (P=0.036). Three patients achieved a VGPR or better in a heavily pre-treated patient group with a 3-year OS of 65%.[43] Grade 3 or greater adverse events (seen in 33%), predominantly cytopenias, were manageable. Bendamustine should be explored earlier in the disease course.

Immunomodulatory agents

The efficacy of immunomodulatory (IMiD's) agents in plasma cell dyscrasias opened up another treatment avenue for AL amyloidosis. Thalidomide, the first of these agents, has a limited role in AL amyloidosis as monotherapy due to unacceptable toxicity at higher doses and limited efficacy.[68] The combination of thalidomide and dexamethasone (median thalidomide dose 300 mg) was effective and with clonal response rates of 48% (n=31), CR in 19%, and organ response in 26%. The median time to response was 3.6 months[69] but 60% experienced grade 3 or greater toxicity.

In the UK, a risk-adapted strategy based on the patient's clinical status allowed use of dose-adapted CTD (cyclophosphamide/thalidomide/dexamethasone) with good and rapid hematologic responses[20] seen in 74%, with CR and PR in 21% and 53%, respectively, and organ responses in 33%. A recent analysis of a larger cohort of 202 patients confirmed these findings[55] (Figure 4C). Prospective analysis suggests that toxicity of CTDa still remains high with 60% experiencing grade 3 or greater toxicity (mainly fluid overload).[70] This regime was the standard of care in the UK but bortezomib-based regimes are increasingly being used.

Lenalidomide is a second generation IMiD with greater anti-myeloma efficacy and favourable toxicity profile. Two phase II studies reported that lenalidomide-dexamethasone (Len/Dex) treatment showed good hematologic responses in 67% (n=24), with CR and PR in 29% and 38%, respectively.[36,37] Standard lenalidomide doses of 25 mg were poorly tolerated with much better tolerance with 15 mg daily. The most common side effects were fatigue and myelosuppression accounting for 35%, and thromboembolism in 9% (n=3). Skin rashes were experienced in 43%.[71] Lenalidomide combined with dexamethasone has been used in a small cohort of patients refractory to alkylators, bortezomib and thalidomide, with a 41% response rate and survival advantage in responders, indicating that IMiDs can have a role in salvage treatment,[72] with no increased incidence of secondary malignancies.[73]

Complete response rates remain low with lenalidomide-based regimens and a number of phase II studies have focused on addition of an alkylator to improve the response rates.[24,38-41] Studies with additional cyclophosphamide or melphalan report overall hematologic response rates of 55-60% and CRs of approximately 20%. The toxicity of the combination is high with nearly two-thirds of patients reporting grade 3 or greater toxicity including hematologic in 46%; other side effects including fatigue, edema and gastrointestinal problems. The response rates in advanced stage patients are poor.[24,41] The exact role for a lenalidomide-alkylator combination and advantages offered over Len/Dex remain to be clearly defined.

Pomalidomide (a 3rd generation IMiD effective in myeloma refractory to lenalidomide) with dexamethasone achieved hematologic responses in 48% of patients with refractory AL[44] with organ responses in 5 patients. The median OS and PFS were 28 months and 14 months, respectively. A third of all patients withdrew from the study due to adverse events. Pomalidomide shows promise as salvage therapy in relapsed refractory patients and its combination with proteasome inhibitors needs to be explored further.

IMiDs, although effective and an important part of the treatment in AL amyloidosis, for unknown reasons, are poorly tolerated in AL compared to multiple myeloma with fluid retention, fatigue and a recently identified phenomenon of a paradoxical increase in cardiac biomarkers during therapy;[74] all these issues need further study. The latter is of particular significance given its role in assessing cardiac responses in AL amyloidosis although a rise in the NT pro-BNP following the first cycle of lenalidomide was not associated with poor survival or renal deterioration.[24]

Proteasome inhibitor-based regimes

Bortezomib-based regimens have changed the treatment paradigm in AL amyloidosis over the last few years. Plasma cells in AL amyloidosis appear to be especially sensitive to proteasome inhibitors in a pre-clinical model;[75] the accumulation of pre-fibrillar light chains after proteasome inhibition adding to the cellular toxicity. The high response rates and good tolerance have led to bortezomib combinations being adopted as front-line therapy in AL amyloidosis. Prospective evidence of superiority or better tolerability over current standard regimens, particularly in elderly subjects with advanced cardiac disease, is still lacking.

A multicenter retrospective analysis of 94 patients showed high hematologic response rates (71%) achieved rapidly (a median response time of 52 days) with associated organ responses in 30%. The 1-year survival rate was

76%. One-third experienced grade 3 toxicity and the most common non-hematologic side effects included peripheral sensory neuropathy, orthostatic hypotension, gastrointestinal disturbance or peripheral edema.[32] A prospective phase I/II trial confirmed the high response rate and reported similar efficacy in patients with relapsed refractory AL amyloidosis with both once (OW) or twice (TW) weekly schedules in 70 patients.[31] Hematologic response, median time to best response, one year PFS and grade 3 or greater toxicities were 68.8%/66.7%, 3.2/1.2 months, 72.2/74.6% and 50%/79%, respectively, in the OW and TW groups.[31]

A number of groups, including our own, have now studied bortezomib with additional cyclophosphamide (CyBorD) or melphalan (BMDex) in AL amyloidosis.[34,76] Of 17 patients receiving CyBorD at the Mayo Clinic (58% with symptomatic cardiac involvement), a clonal response was achieved in a median of 2 months in 94%, with 71% and 24% achieving a CR and PR, respectively.[34] In the UK, 43 patients received CyBorD (bi-weekly bortezomib) (74%; cardiac involvement and 46% stage III by the Mayo cardiac staging), with overall hematologic response rates of 81% (CR 42%).[33] The estimated 2-year PFS was 66% and 41% for front-line treatment and relapsed setting, respectively. The estimated 2-year OS was 98%.[33]

BMDex has been studied in a prospective trial in the US77 and in a retrospective cohort in Italy.[50] An early report from the prospective study has shown a 94% hematologic response rate with 38% CRs. However, in the retrospective study, hematologic response rates were 48% (CR 18%, VGPR 21%) with BMDex and the absolute dFLC decrease in responders 95%, significantly greater than those treated with MDex (median 83%; P=0.018). The lower overall response rate in this study was due to early deaths in cardiac patients and similar results now reported with larger CyBorD treated cohorts,[78] highlighting a possible concern using bortezomib in advanced cardiac disease. A randomized prospective trial is ongoing in Europe and Australia comparing MDex with BMDex. Ixazomib and carfilzomib are novel proteasome inhibitors appearing to have greater efficacy of proteasome inhibition compared with bortezomib with a more favorable toxicity profile. A phase I study of ixazomib has been completed with good tolerance and responses seen in multiple refractory patients.[79] A phase III trial is ongoing.

Allogeneic stem cell transplantation

Allogeneic stem cell transplantation is not widely used in AL amyloidosis. Following the first successful case, reported in 1998,[80] a European Group for Blood and Marrow Transplantation (EBMT) registry study in 2005 reported 19 patients with AL amyloidosis (7 patients full intensity conditioning; 8 reduced intensity conditioning (RIC)). The overall and progression free survival was 60% and 53%, respectively, at one year, with TRM of 40% (TRM 50% in patients receiving total body irradiation). Ten patients achieved hematologic responses and 8 attained organ responses.[81] Anecdotal reports suggest RIC-SCT is possible in AL.[82] Currently, allogeneic stem cell transplantation may have a role in highly selected young fit patients with relapsed disease but, ideally, should only be considered in the context of a clinical trial.

An approach to treatment

The treatment strategy in a patient with AL amyloidosis is shaped by poignant background factors including age, co-morbidities, performance status, contraindications to drugs and patient preference deciding the ultimate choice of the regimen, especially in the lack of clear randomized evidence. Figure 5 provides a suggested treatment algorithm for patients treated outside of clinical trials. The choice of up-front treatment is between autologous stem cell transplantation (ASCT) and combination chemotherapy, one not necessarily precluding the other. Patients with good performance status, limited organ involvement, good renal function, cardiac ejection fraction over 50%, CO diffusion capacity over 50%, cardiac troponin T below 0.06 ng/L and NT-proBNP below 5000 ng/L appear to have a less than 5% TRM during ASCT57,[83,84] and should be offered ASCT as a treatment choice. Borderline patients treated with a stem cell sparing regime with improved organ function may allow ASCT at a later date. Bortezomib has emerged as the backbone of induction regimens; CyBorD or BMDex are becoming the regimens of choice in most non-neuropathic patients. Cautious low-dose regimens are needed in advanced cardiac involvement (especially with NT-proBNP >8500ng/L). Patients with neuropathy pose a dilemma, with melphalan/dexamethasone or lenalidomide/dexamethasone as suitable up-front treatments. Response reassessment at the 3-month point interval is key; patients with a poor response should be considered for either dose increments or an additional drug to improve the response.

Best organ responses occur in those achieving a hematologic CR/VGPR, but partial responders may also achieve an organ response. Lenalidomide and pomalidomide-based regimens or bendamustine are useful in the relapsed/refractory setting. The value of alkylator-based regimes in patients relapsing after a novel agent-based regime is uncertain.

IgM associated AL amyloidosis

Of all patients with amyloidosis, 4-7% have an IgM secreting (mainly) lymphoplasmacytic lymphoma (LPL) as the underlying cause of AL.[85,86] Treatment should be directed toward the LPL clone. Single agent alkylators have limited efficacy. Regimes such as melphalan/dexamethasone (n=14), purine analogs (n=17) confer good hematologic responses of 64% and 73%, respectively.[85,86] Recently, rituximab/bortezomib/dexamethasone shows promise, with overall hematologic responses of 78% (n=7).[87] Larger clinical trials are needed to evaluate this further.

Organ transplantation

Organ transplantation can be considered in patients attaining a vGPR or better with irreversible end-stage organ function, or in a situation to facilitate aggressive chemotherapy, not otherwise feasible due to organ dysfunction. Long-term control of the underlying clonal disorder is needed to prevent recurrence after organ transplantation or progression in other organs.

Cardiac transplantation may be the only option to improve survival in younger patients with advanced isolated heart involvement, accounting for 0.14% of heart transplants nationwide according to the United Network for Organ Sharing (UNOS).[88] A UK study reported 24 patients from 1984 to 2002 undergoing heart transplantation in 6 UK cardiac transplant centers, 17 diagnosed with AL amyloidosis. The 1- and 5-year OS was 50% and 20%, respectively, not receiving chemotherapy *versus* 71% and

36% who did.[89] Another multicenter study of 69 patients receiving heart transplants for amyloidosis (all types), reported 1- and 5-year survival of 74.6% and 54%, respectively.[88] Control of the underlying clone is important, and ASCT is generally considered most appropriate treatment. One US series between 1994 and 2005 included 11 patients undergoing the two procedures serially. Nine patients survived both with 3 eventually dying due to progressive amyloidosis, the earliest 55 months post ASCT. The 1- and 5-year survival following heart transplantation in this cohort was 82% and 65%, respectively,[77,90] a marked improvement over the otherwise median survival of advanced cardiac AL of 3-8 months. Scarcity of organs, risk of amyloid recurrence, and higher mortality of amyloid patients undergoing heart transplants still makes cardiac transplantation a contentious issue.[88]

Renal transplantation in AL amyloidosis is considered to improve long-term survival and quality of life. The largest UK series reports 22 patients undergoing renal transplantation; (19 cadaveric donors and 3 live donors), and 3 with extra-renal organ dysfunction. Nineteen patients received chemotherapy or ASCT, 74% achieving a hematologic response (11 PR and 3 CR) with no graft failures secondary to amyloid recurrence and 1- and 5-year OS 95% and 67%, respectively.[91] The Mayo group reported 19 patients receiving renal transplantation (1 cadaveric donor and 18 live donors), 12 having extra-renal involvement from 1999 to 2008. All attained a hematologic response (18 CR and 1 PR), 8 receiving renal transplantation followed by ASCT, 6 receiving ASCT followed by renal transplantation, and 5 receiving non-myeloablative chemotherapy followed by renal transplantation, with no significant difference between these groups. The 1- and 5-year OS was 84% and 76%, respectively.[91] Good long-term outcomes appear to be associated with renal transplantation in AL in highly selected cases.

Outcomes with orthotopic liver transplantation (OLT) for advanced liver AL remain poor. A UK study from 1984 to 2009 included 9 patients undergoing an OLT with the 1- and 5-year survival from transplantation 33% and 22%, respectively.[91]

Novel therapies for amyloidosis

A number of therapies are in development targeting various components of the pathophysiology of amyloid fibrillogenesis. Glycosaminoglycans are a universal constituent of all amyloid deposits and inhibition of the interaction between GAGs and amyloid fibrils. This is a promising therapeutic approach AA type which may also have merit in AL. Eprodisate (Kiacta®, Bellus Health, Canada) is a negatively charged, sulfonated molecule of low molecular weight and is undergoing phase III trials.[92] There is growing interest in developing therapeutic antibodies to directly target amyloid deposits. Mu 11-1F4 is a chimeric antibody reactive with many AL fibrils,[93] localization of which has been studied in patients with PET imaging.[94] Its administration as a therapeutic is planned. mAb2A4 is another monoclonal antibody, binding AL/AA fibrils and human AL amyloid extracts,[95] reported to cause amyloid regression in mouse models of AA and AL amyloidosis. This antibody has been further developed as NEOD001 (Onclave Therapeutics Limited, CA, USA), recently commencing phase I trials in systemic amyloidosis in the US. Pre-clinical development of small interfering RNAs (siRNAs) has also been explored as a treatment in reducing the expression of the amyloid precursor protein, with in vitro studies showing inhibition of synthesis of light chains in transfected cells, and *in vivo* reducing the production and circulating free light chains.[96]

R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC) is a drug which cross-links pairs of SAP molecules *in vivo*[97] resulting in rapid clearance of SAP from the liver and almost complete depletion of plasma SAP.[98] Some SAP persists on the amyloid deposits, and lack of plasma SAP allows administration of an anti-SAP antibody which can now target the amyloid deposits. Following promising results in transgenic mouse model of AA amyloidosis, using anti-SAP immunoglobulin-G (IgG) antibodies and CPHPC,[99] early phase clinical trials are underway to explore this further with initial patient recruitment commencing this year.

Conclusion

AL amyloidosis is rare. It is frequently diagnosed late due to the subtle signs and symptoms of the disease. Increasing awareness of this disease poses major challenges. Improved diagnostic techniques have enabled better detection of this disease. Risk stratification using cardiac biomarkers has refined treatment selection and reduced morbidity and TRM. Diagnosis and treatment planning in AL is complex and best considered in specialist centers that have the expertise of a multi-disciplinary team. Novel agent-based chemotherapy, especially with bortezomib, has improved chemotherapy responses and is being explored pre- and post-ASCT. Bendamustine, lenalidomide and pomalidomide are valuable therapies for relapsed refractory patients. Good hematologic responses (attaining at least a vGPR being the goal of therapy)[22] translates into organ responses and improved survival. While cardiac and hematologic responses can be simultaneous, responses of other organs may evolve over months or years. Early mortality of patients with advanced disease persists. Future directions involving therapies targeting the amyloid deposits - anti-fibril antibodies are in early phase trials. Exploring the role of minimal residual disease, the importance of eradicating this and gaining insight into the microenvironment are needed. Ultimately, the most important factor is increasing awareness to ensure early diagnosis to allow therapy before extensive organ involvement.

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