International Journal of Hematological Disorders, 2014, Vol. 1, No. 1A, 21-29
Available online at http://pubs.sciepub.com/ijhd/1/1A/4

DOI:10.12691/ijhd-1-1A-4

Light Chain Amyloidosis 2014

Moshe E. Gatt*

Department of Haematology, Hadassah Hebrew University Medical Center, Jerusalem, Israel
*Corresponding author: Rmoshg@hadassah.org.il

Received September 25, 2014; Revised November 11, 2014; Accepted December 09, 2014

Abstract AL amyloidosis patients are difficult to diagnose. Patients having multi-organ and particularly cardiac involvement are considered to have bad prognosis. Early diagnosis is therefore essential. Treatment is to be given according to risk. The use of autologous stem cell transplantation is associated with unacceptable toxicity in high-risk patients. Low risk and some intermediate risk patients may benefit from it with responding patients having prolonged overall survival. New medications, such as thalidomide, lenalidomide and bortezomib, and next generation IMiDs and proteasome inhibitors are derived from multiple myeloma regimens. Their combination with dexamethasone and alkylating agents have a profound effect even in transplant ineligible patients.with surviving patients having excellent progression-free and overall survival, even in a significant proportion of high risk, poor prognosis populations. This review includes the latest updates on treatment for AL amyloidosis patients in 2014, in light of the progress done during the recent years.

Keywords: *Amyloidosis, therapy, novel- agents*

Cite This Article: Moshe E. Gatt, "Light Chain Amyloidosis 2014." *International Journal of Hematological Disorders*, vol. 1, no. 1A (2014): 21-29. doi: 10.12691/ijhd-1-1A-4.

1. Introduction

Amyloidoses are a group of diseases sharing common tertiary protein structure. The protein misfolding causes aggregation and tissue deposition of the proteins. In the case of systemic immunoglobulin light chain amyloidosis (AL), the monoclonal light chains are produced by a bone marrow plasma cell clone which aggregates in vital organs [1,2]. Plasma cell dyscrasias include several diseases, discriminated by their end-organ damage. In multiple myeloma (MM) the patients will have a rapid-proliferative disease and suffer of myeloma end-organ damage such as bone lesions, anemia and tubular kidney disease. In AL the clone is small, and the clinical scenario and prognosis correlate directly to the organ dysfunction caused by the amyloidogenic light chain [2]. Being a plasma cell related disorder, AL may be found secondary to MM in 10-15% of patients, conferring worse prognosis [3,4,5,6]. However, if found incidentally with no AL organ damage, prognosis is dependent on the MM primary disease as reported by retrospective series [7,8], whereas others do show such clinical significance [9]. Primary AL rarely progresses to overt active MM [5]. Treatment of primary AL is derived of MM treatments with the usage of chemotherapy and more recently novel agents to eliminate the neoplastic clone [10].

Much research has been performed to determine the molecular factors that make a particular LC protein amyloidogenic, to elucidate the mechanism of amyloid fibril formation, and even to characterize the amyloid formation in-vitro [11,12,13]. It is very likely that factors in the patient, including nutrients and antioxidants will affect amyloidogenicity as well [12,13]. Studying the biology is therefore complicated in designing proper experiments, addressing the molecular level of the phenomenon in-vitro and undoubtedly in-vivo.

There is a strong debate regarding the mechanism by which amyloidosis causes organ damage and dysfunction. Lessons learnt from clinical observations at least in AL, raise the hypothesis that it is not solely the deposition of amyloidogenic material in the tissues causing organ injury [13,14,15], but more so the LC toxicity is the central setback.

Amyloid LC precursors are likely to mediate cellular toxicity through a mechanism that causes oxidative stress and activates the apoptotic pathway thus being directly cytotoxic [16]. Effective immunotherapy and chemotherapy induces a rapid and simultaneous reduction of the concentration of the circulating amyloidogenic free light chains (FLC) with improvement of heart failure symptoms and prolonged survival [17,18], thus indicating that LC oligomers and/or nascent amyloid fibrils may significantly contribute to amyloid cardiotoxicity in addition to any mechanical effects of amyloid fibril deposition. Partially because of research limitations, therapy of AL presently is limited to the use of anti myeloma drugs given in MM with considerable toxicity [15].

2. Diagnosis

Diagnosis of AL may be misleading and is usually late in the course of the disease, when the patient is already symptomatic [1]. The category of systemic amyloidosis is determined by the type of protein precipitate. The most common of these is AL: light chains amyloidosis. Among

the other types which may mimic the signs and symptoms of AL- such as the inflammatory amyloidosis [AA Amyloidosis], familial amyloidosis- most commonly transthyretin [TTR Amyloidosis], and amyloidosis of aging [Senile Amyloidosis] - In the case of AL, the plasma cell clone may not be as large as in MM, and may be difficult to differentiate from a benign plasma cell disorder such as monoclonal gammopathy of unknown significance (MGUS) [1,19,20,21]. Even more complicated is the rare situation where a non-AL systemic amyloidoses have overlapping clinical presentations and occurs in the presence of MGUS, which is highly prevalent [19,20,22]. Thus demonstrating that amyloid deposits are formed by light chains before starting treatment for AL amyloidosis is mandatory. This should be done by either performing a biopsy of an available indirect involved organ (i.e.- fat pad aspirate or biopsy) or by biopsy of the targeted organ itself [2,23].

Light microscopy immunohistochemistry can consistently identify AA amyloidosis, but LC immunohistochemistry is unreliable [24]. Immuno electron microscopy performed on abdominal fat aspirates and organ biopsies is done at specialized centers [25]. Other highly sensitive methods being done at large centers are laser capture microdissection [26] with mass-spectrometry identification.

AL amyloidosis is a hematologic malignancy. However, its manifestations are mostly non-hematologic, making the diagnosis delayed even in subjects with preexisting plasma cell dyscrasia [27]. Clinically, for the most part, AL amyloidosis is a multisystem disease manifested in a wide range of clinical signs. It may involve almost every organ but for the central nervous system, and most commonly are the kidneys and the heart. Early diagnosis and accurate treatment may prevent the formation of irreversible damage, and decreasing the LC levels in the blood can lead within a few months to a dramatic improvement in organ function. Therefore it is highly important to have a high level of awareness to diagnose promptly and properly, albeit its rarity (prevalence of 1: 100 000 people) [2].

3. Common Clinical Syndromes in AL Amyloidosis

Essentially every organ, except the central nervous system, may be involved in primary amyloidosis. Outlined are the major syndromes [1,2,11,19,28,29,30,31,32] and clues for elevated suspicion (Table 1):

Cardiac: amyloid infiltration of the heart causes septal thickening and the development of ventricular failure, particularly diastolic. Hypertensive heart disease echocardiography studies may be similar, yet in contrast to amyloidosis, the electric complexes will be enlarged, whereas small or normal in AL. Typical signs will be seen by strain echo Doppler [33] and cardiac MRI that may distinguish between the two entities [34]. Patients are dependent on cardiac filling pressure, thus medications such as beta-blockers, calcium and angiotensin inhibitors may aggravate the clinical heart failure. Digoxin is forbidden due to increased toxicity. Increase in the cardiac biomarkers N-terminal pro-natriuretic peptide type-B (NT-proBNP) and troponins [35,36], allow sensitive and accurate assessment of the extent of involvement, the prognosis, as well as evaluating the response to treatment. The presence and extent of heart involvement is the major prognostic determinant. Without treatment, most patients will die within six months. A staging system (Table 2) based on these biomarkers [37], recently revised [38], allows accurate discrimination of low-risk (who are candidates for aggressive treatment and also have prolonged survival if they respond to therapy), intermediate-risk, and high-risk (who are very fragile and often die before having a chance to respond to therapy) patients. Furthermore, hematologic response is assessed by measuring changes in the concentration of circulating free light chains, and cardiac response and progression are defined by decreases or increases in NT-proBNP (Table 2) [39,40]. Since AL amyloidosis is a rapidly progressive disease, response to treatment needs to be assessed early, in order to rapidly start rescue therapies in non-responders to prevent further damage.

Table 1. Signs that should increase a suspicion to the presence of AL amyloidosis in accordance to organ involvememnt

Signs that should raise a suspicion to the presence AL amyloidosis	
	Attention to details and a high level of suspicion is the key to diagnosis
General	AL amyloidosis is a multi-system disorder. A combination of unexplained symptoms in a number of central organs/ systems should raise a suspicion for a rare disease.
Cardiac	Thickening of the ventricular septum in the presence of normal-sized ventricle or small complexes with electrocardiographic signs of hypertrophy.
Renal	Proteinuria without a clear explanation, and normal kidney size or large kidney size.
	Albuminuria without a clear explanation, even in the presence of comorbidities such as diabetes and hypertension, but without the expected disease-related retinopathy
Cardiac and Renal	Unexplained peripheral edema
Dermal	Dermal bleeding tendency without a source, with no hematologic clotting abnormalities
Peripheral nervous system	Peripheral neuropathy with no source
	Bilateral carpal tunnel syndrome
	Unexplained orthostatic hypotention
Gastrointestinal	Gastrointestinal disorders - constipation or diarrhea, unexplained weight loss.

Renal: The kidneys are the most involved organ in AL amyloidosis, but rarely involved in various forms of familial amyloidosis. The disease typically causes glomerular injury [41]. Therefore, albuminuria is the most common manifestation of renal involvement, occasionally to a nephrotic range. Blood creatinine increased only with advanced stages. Renal ultrasound scan will usually normal in size and sometimes larger than normal (as opposed to chronic failure due toother diseases where the kidneys are usually undersized). Difficult to differentiate, albuminuria commonly exists in the background of renal dysfunction secondary to diabetes and hypertension. Note that in these cases there will also be the characteristic ocular matching retinopathy. The presence of a paraprotein and albuminuria in these co morbidities, in the absence of retinopathy, is suggestive of amyloidosis [2,41].

As with cardiac injury, early detection and effective treatment may prevent deterioration of renal function, need for dialysis, and improve and even cure the proteinuria. Angiotensin inhibitors are of little value, and given the damage to cardiac and autonomic function, may worsen the patient's condition.

Table 2. Updated International Society of Amyloidosis criteria for Cardiac staging and for haematologic and cardiac response

Standard staging system [37]	The system is based on NT-proBNP (cutoff 332 ng/L) and cTnT (cutoff 0.035 ng/mL). Stage I, II, and III, patients have none, one or two markers above the cutoffs, respectively.
Revised staging system [38]	The revised staging system is based on NT-proBNP (cutoff 1800 ng/L), cTnT (cutoff 0.025 ng/mL), and dFLC (cutoff 180 mg/L). Stage I, II, III, and IV patients have none, one, two or three markers above the cutoffs, respectively.

Type of response [143]	Definition
Complete response	Negative serum and urine immunofixation and normal FLC κ/λ ratio
Very good partial response	dFLC <40 mg/L
Partial response	dFLC decrease >50%
No response	other
NT-proBNP response*	>30% and >300 ng/L reduction in subjects with baseline NT-proBNP≥650 ng/L

dFLC, difference in concentration between involved (amyloidogenic) and uninvolved free light chain; eGFR, estimated glomerular filtration rate; FLC, circulating free light chain; iFLC, involved (amyloidogenic) free light chain; NT-proBNP, N-terminal natriuretic peptide type-B; cTnI /cTnT, cardiac Troponin I / T

*Caution should be used in interpreting NT-proBNP changes in subjects treated with immune modulatory drugs and in those with a >25% decrease in glomerular filtration rate.

Peripheral nervous system: neuropathy may be the initial finding of primary AL amyloidosis. It may be characterized by autonomic nervous system dysfunction with diarrhea (or constipation), a low blood pressure (positional) or men's erectile dysfunction. Patients with a history of high blood pressure, gradually become balanced or even with low blood pressures. Carpal Tunnel Syndrome, for example, when it appears two-sided, should raise the alarms for an infiltrative disorder, due to nerve injury and soft tissue thickening.

Liver and Digestive System: Hepatic involvement in most cases is asymptomatic, despite the increase, sometimes significantly, of the liver enzymes. Laboratory tests show an increase ofespecially alkaline phosphatase [2,23,32,41]. Amyloidosis associated with diarrhea is in the most part of the autonomic nervous system malfunction. Amyloid deposits may present anywhere in the gastrointestinal tract, causing bleeding or malabsorption of food products. Altered taste and difficulty in eating solid foods are hallmarks of base of the tongue enlargment. Splenomegaly may result in binding of factor X to the amyloid deposition, extending the laboratory time PT or PTT coagulation tests, with a tendency for spontaneous bleeding.

Soft tissue and skin: cutaneous manifestations of primary amyloid may provide important clues towards the diagnosis, especially when other organ involvement suggest the presence of a systemic disease [2,23,32,41]. Cutaneous involvement is limited almost exclusively to AL amyloidosis among another amyloidoses. However, these appear only in 10-15% of patients. The disease can manifest itself among other appearances by subcutaneous nodules called Amyloidomas.

4. Treatment

Being a rare disease, large controlled patient trials of primary AL are difficult to conduct [42]. As many patients have multi-organ dysfunction which renders them more susceptible to treatment toxicity, this should always be kept in mind in designing the therapeutic strategy. Good responses to therapy on one hand, and the patients' sensitivity to various agents on the other, raise the question of which strategy is the best to choose for the newly diagnosed or relapsed AL patient. Thus, various reports are of single arm trials with different populations which are difficult to compare [43]. All treatments are aimed at the elimination of the plasma cell clone [44]. These include conventional dose chemotherapy (mostly melphalan), high dose chemotherapy and novel agents combinations.

Conventional-dose therapy: Melphalan, an alkylating agent, has been adapted from the historical use in MM, and shown to be safe and effective in AL [45]. However, deep responses are rare (~30%) and are reached slowly [45,46]. Oral melphalan and dexamethasone (MDex) in patients who are not eligible for autologous stem cell transplantation (ASCT), obtained encouraging hematologic response rates of 67% (complete remission (CR) 33%), with a low 4% treatment related mortality (TRM) [47,48]. The median survival of patients treated with MDex was 5.1 years, thus leading to be a widely acceptable first line treatment [43].

However, cardiac patients with advanced heart involvement did not tolerate high-dose dexamethasone, and lowering the dose from 40 to 20 mg on days 1-4 was associated with a significantly lower CR rate (16% vs. 31%) [49]. Other trials of MDex in patients with advanced cardiac involvement show worse outcomes (only 44% hematologic response) and a high treatment related mortality (TRM) rate of 26% of patients. [50], with a very short median survival in another trial [51]. In addition, intermediate dose intravenous melphalan results in significant toxicity [52,53]. Thus melphalan cannot overcome the poor prognosis of subjects with advanced cardiac involvement, and although no randomized trial has been published, newer agents and combination treatments are showing promising superior results.

Autologous stem cell transplantation: ASCT was first published in 1998 as a major breakthrough in the treatment of AL amyloidosis [54], following its use in MM. Melphalan 200 mg/m^2 was reported to induce 76% haematologic response rate, and additionally a CR in 33% of patients, while TRM was 12-13% [55,56,57], but can be as high as 40% TRM in a multicenter settings [58]. Reduction of the melphalan dose may be suitable for patients with moderate cardiac dysfunction, but results in some lower hamatologic response rates, and a varying TRM rates, which may still be high [55,57,59,60,61,62]. The total number of patients in each trial group was low, thus highlighting the difficulty of comparison among patient groups. Overall, there is no evidence that reduced-intensity ASCT (melphalan 100-150 mg/m^2) is superior to non-myeloablative chemotherapy in AL amyloidosis, while retaining a significant TRM.

Another major difficulty encountered is a high initial mortality rate (17%) during induction chemotherapy and during the period of stem cell mobilization [63]. Giving induction chemotherapy as done in MM before ASCT, resulted in no benefit.

The only head-to-head randomized controlled trial evaluation MDex vs. ASCT, failed to demonstrate an advantage in terms of hematologic response rate (67% vs.

68%) for ASCT over MDex [64]. TRM was relatively high (24%), perhaps obscuring the beneficial effects of ASCT, and possibly a higher risk patient population was present. Nonetheless, the last updated results, with a longer follow-up of > 5 years after last recruitment, did not find any superiority in the intensive arm in survival or remission duration, even in the landmark analysis eliminating TRM [65].

Since then, efforts were made to improve selection of candidates for ASCT and to stratify them according to risk [32,66]. Refinement of eligibility criteria since 2009 resulted in a marked decrease of TRM (10.5% vs. 1.1%) [67,68], concluding that Patients with serum troponin T >0.06 ng/mL or NT-proBNP >5000 pg/mL (not on dialysis) should not be considered candidates for ASCT because of early mortality. An update on survival for patients attaining CR post ASCT show the estimated probability of survival for patients in CR was as high as 86% at 5 years. Patients who did not achieve a CR had a short median EFS of 2 years (CI 95% 1.6–2.7), as compared with 8.3 years for patients in CR ($p<0.0001$) [60,69]. In another series with long term follow up, 44% of patients survived more than 10 years (Cordes, *et al* 2012).Interestingly, patients with AL have a significantly better prognosis than parallel MM patients receiving ASCT [70]. Accurate baseline risk assessment of cardiac biomarkers is thus the cornerstones for careful patient selection. Consequently, only a minority of patients (20-30%) will be eligible for ASCT. Overall these promising results in well selected patients show that ASCT may still be an established first line modality in low-intermediate risk AL patients.

Lately, conditioning regimens incorporating Bortezomib to the treatment resulted in improved disease free and overall survival without affecting engraftment [71]. Therefore it may be advisable to combine ASCT with a short course of a bortezomib-based protocol either before or after transplantation.

Allogeneic and Organ transplantation: Transplantation of the organs involved by amyloidosis may prolong survival and allow patients with advanced disease to be eligible for treatment. Organ transplant can be considered in patients who attain CR, but have irreversible end-stage organ damage. Available data indicate that kidney transplant can be offered to patients with AL amyloidosis with sustained CR [72]. Heart transplant followed by ASCT or other effective chemotherapy can be the only effective option for young patients with isolated, severe cardiac involvement [73-78]. It is limited by the graft availability, and patients may die while waiting for organs [79]. Allogeneic bone marrow transplant has been associated with a very high (40%) TRM [80] and thus is not a preferred option in AL patients.

Novel agents: Novel agents employed in MM treatment, have made their way into the AL therapeutic setting. The introduction of thalidomide, lenalidomide and bortezomib over the last decade has been suggested to improve patient outcome and overall survival including higher risk patients than those included in ASCT trials [32,44]. However, these encouraging data are based on clinical trials with a selected population of patients and retrospective cohorts, some of which were performed in AL- specialized centers. “Real-world" reports, assessing the tolerability and efficacy of these new treatments in non-selected populations [43,81,82] show a wider range of responses. In addition, most trials include both newly diagnosed and relapsed/refractory patients, and long term follow up is limited.

IMiDs: Thalidomide: Thalidomide with or without dexamethasone has limited efficacy in AL [83,84,85]. Toxicity was substantial, with 65% of subjects experiencing serious adverse events (SAE), including symptomatic bradycardia (26%), fatigue and constipation [85]. Combined with melphalan and attenuated dexamethasone, still resulted in relatively low response rates and high adverse events [86]. The addition of cyclophosphamide to thalidomide and dexamethasone (CTD) resulted in a 74% haematologic response rate (CR in 21%) [87]. The "real world" prospective follow up ("Alchemy registry") of 250 patients treated as of September 2009, most of whom had received CTD as upfront therapy (77% of patients), demonstrated that although 33% managed to achieve a CR/VGPR, after a median follow up of 7 months, 29% of patients died, and 50% of treated patients had to be hospitalized for treatment toxicities [81]. Renal organ responses were also poor. Most common toxicities were fluid retention and sedation, and TRM was 4%. A recent publication comparing matched patients treated with cyclophosphamide, dexamethasone and either bortezomib or thalidomide, show a similar OS but much better responses 40.5% CR vs 24%, respectively and a PFS 28 vs. 14 months, between the two cohorts [88]. However, an early switch of non-responding 91 patients by 3 cycles of CTD in the "Alchemy" trial, were salvaged by second line therapy (84% bortezomib containing regimens), thus allowing better responses, and consequently prolonged and comparable OS with first line CTD responders [81].

Lenalidomide: It is difficult to separate trials for newly diagnosed and relapsed refractory patients, as those are usually reported together. Doses of lenalidomide higher than 15 mg are poorly tolerated especially in patients with high cTn [89,90] and the hematologic response rates ranged from 41% to 47% [91,92,93].

Lenalidomide combination with an alkylator, mostly cyclophosphamide, and dexamethasone had favorable hematologic response rates ranging from 40% to 77%, being lower in pretreated subjects and CR rates were up to 20%% [94-104]. In all these trials lenalidomide toxicity was prominent (SAE 60-86%) and mainly characterized by cytopenia, fatigue and fluid retention. However, it is a relevant option for patients refractory to bortezomib and other chemotherapeutic agents. Available data indicate that the quality of response to this combination increases over time. To date, there is no information regarding maintenance therapy with lenalidomide.

Pomalidomide: Pomalidomide was tested in heavily pretreated 33 AL patients, also including patients previously treated with thalidomide and lenalidomide, and showed a 48% haematologic response rate, with 3% CR reported [105]. Most patients had cardiac involvement. Treatment was relatively well tolerated, with only 3 patients discontinued therapy due to toxicity.

Safety issues for IMiDs: Concern has risen over possible renal and cardiac toxicity of immune-modulator drugs. In a retrospective analysis from the Boston University group, 66% of patients exposed to lenalidomide developed renal dysfunction, which was reversible in 44% of cases [106]. However, lenalidomide

was reported to be reasonably well-tolerated in patients with associated end-stage renal disease and dialysis [107]. In addition, an increase of cardiac biomarkers BNP and NTproBNP has been reported with the use of IMiDs [96,108,109]. The reason for this phenomenon is not clear. It is usually asymptomatic, and does not imply of treatment failure, but was also correlated with negatively affected survival [109,110]. Thus, in patients taking IMiDs, elevated biomarkers should be followed and assessed as per their dynamics, and not their absolute values [109]. Another safety concern comes from long term follow up of MM patients, showing elevated hazard ratios for secondary malignancies in patients treated with lenalidomide, especially after ASCT with high dose melphalan [111]. Given the prolonged survival in AL after ASCT, this issue should be taken into consideration in the relapsed patients after ASCT setting, even though this was not observed in AL patients to date [112].

Proteasome inhibitors: Proteasome inhibitors, well established in the MM world [113,114], are making their way into the AL setting. The rapid reduction in light chain levels obtained in MM patients receiving bortezomib [1,2,115] prompt its use in AL patients, in whom swift cessation of toxic LC production and precipitation is required in order to prevent and reverse organ damage. Amyloidogenic plasma cells synthesize misfolded light chains, resulting in proteasomal overload, which makes them highly sensitivity to bortezomib [115]. Indeed, bone marrow purified plasma cells derived from amyloid patients are twice as vulnerable to bortezomib inhibition as those obtained from MM patients. Similarly to the observations with lenalidomide, it is difficult to separate trials for newly diagnosed and relapsed refractory patients, as those are usually reported together. Bortezomib as a single agent shows good efficacy of up to 69% hematologic responses and 38% CR rates, and was well tolerated at up to 1.6 mg/m^2 once weekly and 1.3 mg/m^2 twice weekly [116,117,118] Moreover, responses are durable [119]. The combination of bortezomib and dexamethasone (BDex) produced high hematologic response rates (87%-94%) [120,121]. SAE were observed in 29% of cases, most common being fluid retention and hypotension, and TRM was 3% [122].

Adding cyclophosphamide to BDex (CyBorD) yielded an unprecedented VGPR /CR in 16 of 17 treated patients [123,124], with minor toxicity. In 43 patients receiving this combination resulted in hematological remission of 81.4% with CR of 42% (frontline patients, 66.5% CR). These results translated into an estimated 2 year PFS of 98% [125,126]. Patients receiving BDex plus alkylators (17 patients cyclophosphamide and 33 melphalan) resulted in fair responses, mostly in patients with stage I or II cardiac disease, as compared with those with stage III (67% response and 40%, respectively) [127]. In a recent series of 60 stage III patients, this triplet combination showed a hematologic response rate of 68% and the estimated 1-year survival rate for the whole cohort was 57% although 24 patients (40%) died while on therapy [128]. Thus unable to save the poorest risk patients, the combination of bortezomib, cyclophosphamide and dexamethasone can achieve a high number of hematologic and cardiac responses. In all series onset of response was rapid [88].

Of note, in the landmark (matched case-controlled) analysis of 87 newly diagnosed patients treated with BMDex vs. well matched 87 treated patients with MDex,

A higher rate of complete responses was observed with BMDex (42 vs. 19%), but this did not result in a survival improvement in the overall population, i.e. very high risk patients do not benefit from bortezomib addition [129].

Safety issues for bortezomib: Worsening heart failure, has been reported in MM patients [130] and in some patients reported in the reported AL series. Bortezomib's common side effect is peripheral neuropathy. AL patients already suffer from neuropathy, and therefore caution should be employed with its use. In MM [131], and recently in AL [132] subcutaneous administration resulted in a safer neuropathy profile. A phase III trial for relapsed/ refractory patients with a novel oral proteasome inhibitor (MLN9708) is ongoing in multiple centers worldwide.

Combined bortezomib and ASCT: Combined modalities using adjuvant therapy with BDex has been attempted in subjects who obtained less than CR after ASCT substantially improving the quality of response [133]. The overall response rate in patients with residual light chains post transplant achieved 90% deeper response, with 74% achieving sCR (Landau, *et al* 2012) A complementary approach of administering 2 cycles of BDex before and as conditioning for ASCT also yielded very good response rates [134].

5. Treatment Outline for AL Amyloidosis Patients

With the advances in supportive care and effective therapy, survival curves of responding patients are encouraging [32] Over long term follow up, 2118 patients were divided into 4 cohorts based on date of diagnosis; 1966–1976 (n=121), 1977–1986 (n=343), 1987–1996 (n=636) and 1997–2006 (n=1017). The median OS from diagnosis for the four cohorts were 0.9, 1.2, 1.2 and 1.5 years respectively, $P < 0.001$. Nevertheless, from 2003-2006, the OS of 463 patients followed at this time period shows 42% survival at 4 years [135,136]. Thus, early deaths due to advanced, irreversible cardiac dysfunction at presentation remain an unsolved problem [137]. "Real world" reports [81], retrospective, and comparative retrospective studies [32,44,88,128,129,137,138], show that although the advanced treatment has progressed for surviving patients, high risk patients with advanced clinical cardic stage and extremely elevated cardiac biomarkers are not salvaged by these therapies. These observations of early mortality emphasize the need of early diagnosis, and treatments of rapid action in this disadvantaged subset of patients.

To date, there is no consensus regarding the optimal care for newly diagnosed patients**.** Indications for treatment of AL amyloidosis outside clinical trials are given, based on evidence from uncontrolled studies and retrospective series, and previous reviews published in the literature [2,23,32]:

Patients can be divided into three groups according to their cardiac stage: 1). Low risk- with a proBNP<5000 ng/L / troponin < 0.06 ng/ml, no renal failure, and a good performance status. These patients may benefit from ASCT. 2). High risk- patients with NT-proBNP of > 8500

ng/l who have the worst prognosis and all therapies are limited to salvage them as soon as possible, but none has been shown advantageous. These patients should be treated with lower doses of either agents cautiously. 3). Intermediate risk- The patients in between low and high risks. These patients will benefit of an induction with a novel agent, preferably bortezomib and an alkylator, and ASCT considered according to organ involvement and performance status.

Most clinical trials are lacking data as to the duration of treatment using novel agents in AL. In MM, maintenance treatment has been shown to prolong disease free survival and sometimes overall survival [139]. However, AL is usually a consequence of small plasma cell clones [1]. Patients with primary AL amyloidosis, unlike subjects with MM, do not only have a hematologic malignancy, but also have organ damage which makes them more susceptible to treatment-related toxicity. Moreover, it has been shown that subjects who attain CR, do not have a survival advantage over those who reach PR plus a cardiac response defined as NT-proBNP reduction [140]. It remains to be established whether once organ dysfunction has improved, further treatment aimed at improving the quality of response, or even maintenance therapy, will result in improved survival. Early hematologic FLC response re-assessment (after two cycles), and early switch/ addition of therapy according to the response is advocated [32,44,87]. With the advances in response and survival, high and intermediate risk patients may move to a better risk group, subsequently becoming transplant eligible either at remission or at the time of relapse [141].

The future of novel agents holds great promise for newly-diagnosed and for relapsed/ refractory patients. In the next few years, there are multiple agents being tested and re-assessed prospectively [44,142]. Early diagnosis allowing timely intervention remains the major key towards outcome improvement.

References

[1] Merlini G, Stone M. Dangerous small B-cell clones. Blood. 2006; 108: 2520-2530.

[2] Merlini G, Seldin DC, Gertz MA. Amyloidosis: pathogenesis and new therapeutic options. J Clin Oncol. 2012; 29: 1924-1933.

[3] Desikan KR, Dhodapkar MV, Hough A, et al. Incidence and impact of light chain associated (AL) amyloidosis on the prognosis of patients with multiple myeloma treated with autologous transplantation. Leuk Lymphoma. 1997; 27: 315-319.

[4] Madan S, Dispenzieri A, Lacy MQ, et al. Clinical features and treatment response of light chain (AL) amyloidosis diagnosed in patients with previous diagnosis of multiple myeloma. Mayo Clin Proc; 85: 232-238.

[5] Rajkumar SV, Gertz MA, Kyle RA. Primary systemic amyloidosis with delayed progression to multiple myeloma. Cancer. 1998; 82: 1501-1505.

[6] Rajkumar SV, Gertz MA, Kyle RA. Prognosis of patients with primary systemic amyloidosis who present with dominant neuropathy. Am J Med. 1998; 104: 232-237.

[7] Petruzziello F, Zeppa P, Catalano L, et al. Amyloid in bone marrow smears of patients affected by multiple myeloma. Ann Hematol; 89: 469-474.

[8] Siragusa S, Morice W, Gertz MA, et al. Asymptomatic immunoglobulin light chain amyloidosis (AL) at the time of diagnostic bone marrow biopsy in newly diagnosed patients with multiple myeloma and smoldering myeloma. A series of 144 cases and a review of the literature. Ann Hematol; 90: 101-106.

[9] Vela-Ojeda J, Garcia-Ruiz Esparza MA, Padilla-Gonzalez Y, et al. Multiple myeloma-associated amyloidosis is an independent high-risk prognostic factor. Ann Hematol. 2009; 88: 59-66.

[10] Palladini G, Merlini G. Current treatment of AL amyloidosis. Haematologica. 2009; 94: 1044-1048.

[11] Baden EM, Sikkink LA, Ramirez-Alvarado M. Light chain amyloidosis - current findings and future prospects. Curr Protein Pept Sci. 2009; 10: 500-508.

[12] Bellotti V, Chiti F. Amyloidogenesis in its biological environment: challenging a fundamental issue in protein misfolding diseases. Curr Opin Struct Biol. 2008; 18: 771-779.

[13] Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med. 2003; 349: 583-596.

[14] Merlini G, Westermark P. The systemic amyloidoses: clearer understanding of the molecular mechanisms offers hope for more effective therapies. J Intern Med. 2004; 255: 159-178.

[15] Phipps JE, Kestler DP, Foster JS, et al. Inhibition of pathologic immunoglobulin-free light chain production by small interfering RNA molecules. Exp Hematol; 38: 1006-1013.

[16] Diomede L, Rognoni P, Lavatelli F, et al. A Caenorhabditis elegans-based assay recognizes immunoglobulin light chains causing heart amyloidosis. Blood. 2014; 123: 3543-3552.

[17] Palladini G, Campana C, Klersy C, et al. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. Circulation. 2003; 107: 2440-2445.

[18] Palladini G, Lavatelli F, Russo P, et al. Circulating amyloidogenic free light chains and serum N-terminal natriuretic peptide type B decrease simultaneously in association with improvement of survival in AL. Blood. 2006; 107: 3854-3858.

[19] Comenzo R ,Zhou P, Fleisher M, Clark B, Teruya-Feldstein J. Seeking confidence in the diagnosis of systemic AL (Ig light-chain) amyloidosis: patients can have both monoclonal gammopathies and hereditary amyloid proteins. Blood. 2006; 107: 3489-3491.

[20] Lachmann H ,Booth D, Booth S, et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. N Engl J Med. 2002; 346: 1786-1791.

[21] Obici L, Perfetti V, Palladini G, Moratti R, Merlini G. Clinical aspects of systemic amyloid diseases. Biochim Biophys Acta. 2005; 1753: 11-22.

[22] Anesi E, Palladini G, Perfetti V, Arbustini E, Obici L, Merlini G. Therapeutic advances demand accurate typing of amyloid deposits. American Journal of Medicine. 2001; 111: 243-244.

[23] Gertz MA. Immunoglobulin light chain amyloidosis 2013 :update on diagnosis, prognosis, and treatment. Am J Hematol. 2013; 88: 416-425.

[24] Satoskar A, Burdge K, Cowden D, Nadasdy G, Hebert L, Nadasdy T. Typing of amyloidosis in renal biopsies: diagnostic pitfalls. Arch Pathol Lab Med. 2007; 131: 917-922.

[25] Arbustini E, Verga L, Concardi M, Palladini G, Obici L, Merlini G. Electron and immuno-electron microscopy of abdominal fat identifies and characterizes amyloid fibrils in suspected cardiac amyloidosis. Amyloid. 2002; 9: 108-114.

[26] Vrana J, Gamez J, Madden B, Theis J, Bergen Hr, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood. 2009; 114: 4957-4959.

[27] Kourelis TV, Kumar SK, Go RS, et al. Immunoglobulin light chain amyloidosis is diagnosed late in patients with preexisting plasma cell dyscrasias. Am J Hematol. 2014.

[28] Comenzo RL, Zhang Y, Martinez C, Osman K, Herrera GA. The tropism of organ involvement in primary systemic amyloidosis: contributions of Ig V(L) germ line gene use and clonal plasma cell burden. Blood. 2001; 98: 714-720.

[29] Gertz M, Comenzo R, Falk R, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. Am J Hematol. 2005; 79: 319-328.

[30] Gertz MA, Merlini G. Definition of organ involvement and response to treatment in AL amyloidosis: an updated consensus opinion. Amyloid. 2010; 17: 48-49.

[31] Madan S, Dispenzieri A, Lacy MQ, et al. Clinical features and treatment response of light chain (AL) amyloidosis diagnosed in patients with previous diagnosis of multiple myeloma. Mayo Clin Proc. 2010; 85: 232-238.

[32] Merlini G, Wechalekar AD, Palladini G. Systemic light chain amyloidosis: an update for treating physicians. Blood. 2013; 121: 5124-5130.

[33] Koyama J, Falk R. Prognostic significance of strain Doppler imaging in light-chain amyloidosis. JACC Cardiovasc Imaging. 2010; 3: 333-3.42

[34] Sher T, Gertz MA. Recent advances in the diagnosis and management of cardiac amyloidosis. Future Cardiol. 2014; 10: 131-146.

[35] Palladini G, Campana C, Klersy C, et al. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. Circulation. 2003; 107: 2440-2445.

[36] Dispenzieri A, Kyle R, Gertz M, et al. Survival in patients with primary systemic amyloidosis and raised serum cardiac troponins. Lancet. 2003; 361: 1787-1789.

[37] Dispenzieri A, Gertz M, Kyle R, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol. 2004; 22: 3751-3757.

[38] Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol. 2012; 30: 989-995.

[39] Palladini G, Barassi A, Klersy C, et al. The combination of high-sensitivity cardiac troponin T (hs-cTnT) at presentation and changes in N-terminal natriuretic peptide type B (NT-proBNP) after chemotherapy best predicts survival in AL amyloidosis. Blood. 2010; 116: 3426-3430.

[40] Palladini G, Dispenzieri A, Gertz MAA, et al. Validation of the Criteria of Response to Treatment In AL Amyloidosis. Blood. 2010; 116: 586-587.

[41] Gertz MA, Leung N, Lacy MQ, et al. Clinical outcome of immunoglobulin light chain amyloidosis affecting the kidney. Nephrol Dial Transplant. 2009; 24: 3132-3137.

[42] Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain (AL) amyloidosis. Leukemia. 2012.

[43] Gertz MA. I don't know how to treat amyloidosis. Blood. 2010; 116: 507-508.

[44] Gatt ME, Palladini G. Light chain amyloidosis 20 :12a new era. Br J Haematol. 2013; 160: 582-598.

[45] Kyle R, Gertz M, Greipp P, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. N Engl J Med. 1997; 336: 1202-120.7

[46] Skinner M, Anderson J, Simms R, et al. Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. Am J Med. 1996; 100: 290-298.

[47] Palladini G, Perfetti V, Obici L, et al .Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. Blood. 2004; 103: 2936-2938.

[48] Palladini G, Russo P, Nuvolone M, et al. Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. Blood. 2007; 110: 787-788.

[49] Palladini G, Foli A, Milani P, et al. Oral melphalan and dexamethasone for AL amyloidosis: efficacy, prognostic factors and response criteria. Amyloid. 2010; 17: 81-82.

[50] Dietrich S, Schönland S, Benner A, et al. Treatment with intravenous melphalan and dexamethasone is not able to overcome the poor prognosis of patients with newly diagnosed systemic light chain amyloidosis and severe cardiac involvement. Blood. 2010; 116: 522-528.

[51] Lebovic D, Hoffman J, Levine BM, et al. Predictors of survival in patients with systemic light-chain amyloidosis and cardiac involvement initially ineligible for stem cell transplantation and treated with oral melphalan and dexamethasone. Br J Haematol. 2008; 143: 369-373.

[52] Mollee P, Tiley C, Cunningham I, et al. A phase II study of risk-adapted intravenous melphalan in patients with AL amyloidosis. Br J Haematol. 2012; 157: 766-769.

[53] Mollee P, Tiley C, Cunningham I, et al. A Phase II Study of Risk-Adapted Intravenous Melphalan in Patients with AL Amyloidosis. ASH Annual Meeting Abstracts; 118: 3973.-

[54] Comenzo R, Vosburgh E, Falk R, et al. Dose-intensive melphalan with blood stem-cell support for the treatment of AL (amyloid light-chain) amyloidosis: survival and responses in 25 patients. Blood. 1998; 91: 3662-3670.

[55] Gertz M, Lacy M, Dispenzieri A, et al. Risk-adjusted manipulation of melphalan dose before stem cell transplantation in patients with amyloidosis is associated with a lower response rate. Bone Marrow Transplant. 2004; 34: 1025-1031.

[56] Skinner M, Sanchorawala V, Seldin D, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. Ann Intern Med. 2004; 140: 85-93.

[57] Sanchorawala V, Skinner M, Quillen K, Finn K, Doros G, Seldin D. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation. Blood. 2007; 110: 3561-3563.

[58] Moreau P. Autologous stem cell transplantation for AL amyloidosis: a standard therapy? Leukemia. 1999; 13: 1929-1931.

[59] Madan S, Kumar S, Dispenzieri A, et al. Outcomes with High Dose Therapy and Peripheral Blood Stem Cell Transplantation for Light Chain (AL) Amyloidosis with Cardiac Involvement. Blood. 2009: 223-223.

[60] Cibeira MT, Sanchorawala V, Seldin DC, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. Blood. 2011; 118: 4346-4352.

[61] Cohen A, Zhou P, Chou J, et al. Risk-adapted autologous stem cell transplantation with adjuvant dexamethasone +/- thalidomide for systemic light-chain amyloidosis: results of a phase II trial. Br J Haematol. 2007; 139: 224-233.

[62] Sanchorawala V, Hoering A, Seldin DC, et al. Modified High-Dose Melphalan and Autologous Stem Cell Transplantation (mHDM/SCT) In the Treatment of AL Amyloidosis (AL) and/or High-Risk Myeloma (hM): Analysis of SWOG Trial S0115. ASH Annual Meeting Abstracts. 118: 2004-2011.

[63] Schonland SO, Bochtler T, Perz J, et al. Results of two consecutive phase II trials of patients with systemic AL amyloidosis treated with high-dose melphalan after induction and mobilization chemotherapy. Amyloid. 2010; 17: 80-81.

[64] Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med. 2007; 357: 1083-1093.

[65] Jaccard A, Leblond V, Royer B, et al. Autologous Stem Cell Transplantation (ASCT) Versus Oral Melphalan and High-Dose Dexamethasone In Patients with AL (Primary) Amyloidosis: Long Term Follow-up of the French Multicentric Randomized Trial. ASH Annual Meeting Abstracts. 2010; 116: 1344.

[66] Palladini G, Merlini G. Transplantation vs. conventional-dose therapy for amyloidosis. Curr Opin Oncol. 2011; 23: 214-220.

[67] Gertz M, Lacy M, Dispenzieri A, et al. Trends in day 100 and 2-year survival after auto-SCT for AL amyloidosis: outcomes before and after 2006. Bone Marrow Transplant. 2010.

[68] Gertz MA, Lacy MQ, Dispenzieri A, et al. Refinement in patient selection to reduce treatment-related mortality from autologous stem cell transplantation in amyloidosis. Bone Marrow Transplant. 2013; 48: 557-561.

[69] Cibeira MT, Sanchorawala V, Seldin DC, et al. Outcome of Patients with AL Amyloidosis Who Do Not Achieve Hematologic Complete Response After Treatment with High Dose Melphalan and Autologous Transplantation: Results In a Series of 421 Patients. ASH Annual Meeting Abstracts; 116: 2394.

[70] Dispenzieri A, Seenithamby K, Lacy MQ, et al. Patients with immunoglobulin light chain amyloidosis undergoing autologous stem cell transplantation have superior outcomes compared with patients with multiple myeloma: a retrospective review from a tertiary referral center. Bone Marrow Transplant. 2013; 48: 1302-1307.

[71] Landau H, Hassoun H, Rosenzweig MA, et al. Bortezomib and dexamethasone consolidation following risk-adapted melphalan and stem cell transplantation for patients with newly diagnosed light chain amyloidosis. Leukemia. 2012.

[72] Bansal T, Garg A, Snowden JA, McKane W. Defining the Role of Renal Transplantation in the Modern Management of Multiple Myeloma and Other Plasma Cell Dyscrasias. Nephron Clin Pract. 2012; 120: c228-c235.

[73] Gillmore J, Goodman H, Lachmann H, et al. Sequential heart and autologous stem cell transplantation for systemic AL amyloidosis. Blood. 2006; 107: 1227-1229.

[74] Maurer M, Raina A, Hesdorffer C, et al. Cardiac transplantation using extended-donor criteria organs for systemic amyloidosis complicated by heart failure. Transplantation. 2007; 83: 539-545.

[75] Sack F, Kristen A, Goldschmidt H, et al. Treatment options for severe cardiac amyloidosis: heart transplantation combined with chemotherapy and stem cell transplantation for patients with AL-amyloidosis and heart and liver transplantation for patients with ATTR-amyloidosis. Eur J Cardiothorac Surg. 2008; 33: 257-262.

[76] Lacy MQ, Dispenzieri A, Hayman SR, et al. Autologous stem cell transplant after heart transplant for light chain (AL) amyloid cardiomyopathy. J Heart Lung Transplant. 2008; 27: 823-829.

[77] Dey B, Chung S, Spitzer T, et al. Cardiac Transplantation Followed by Dose-Intensive Melphalan and Autologous Stem-Cell Transplantation for Light Chain Amyloidosis and Heart Failure. Transplantation. 2010.

[78] Sattianayagam PT, Gibbs SD, Pinney JH, et al. Solid organ transplantation in AL amyloidosis. Am J Transplant. 2010; 10: 2124-2131.

[79] Gray Gilstrap L, Niehaus E, Malhotra R, et al. Predictors of survival to orthotopic heart transplant in patients with light chain amyloidosis. J Heart Lung Transplant. 2014; 33: 149-156.

[80] Schönland S, Lokhorst H, Buzyn A, et al. Allogeneic and syngeneic hematopoietic cell transplantation in patients with amyloid light-chain amyloidosis: a report from the European Group for Blood and Marrow Transplantation. Blood. 2006; 107: 2578-2584.

[81] Wechalekar AD, Schonland SO, Kastritis E, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood. 2013; 121: 3420-342.7

[82] Gertz MA. Allaying and alleviating amyloid agony and anxiety. Blood. 2013; 121: 3301-3302.

[83] Dispenzieri A, Lacy M, Rajkumar S, et al. Poor tolerance to high doses of thalidomide in patients with primary systemic amyloidosis. Amyloid. 2003; 10: 257-2.61

[84] Seldin D, Choufani E, Dember L, et al. Tolerability and efficacy of thalidomide for the treatment of patients with light chain-associated (AL) amyloidosis. Clin Lymphoma. 2003; 3: 241-246.

[85] Palladini G, Perfetti V, Perlini S, et al. The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). Blood. 2005; 105: 2949-2951.

[86] Palladini G, Russo P, Lavatelli F, et al. Treatment of patients with advanced cardiac AL amyloidosis with oral melphalan, dexamethasone, and thalidomide. Ann Hematol. 2009; 88: 347-350.

[87] Wechalekar A, Goodman H, Lachmann H, Offer M, Hawkins P, Gillmore J. Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. Blood. 2007; 109: 457-464.

[88] Venner CP, Gillmore JD, Sachchithanantham S, et al. A matched comparison of cyclophosphamide, bortezomib and dexamethasone (CVD) versus risk-adapted cyclophosphamide, thalidomide and dexamethasone (CTD (in AL amyloidosis. Leukemia. 2014.

[89] Palladini G, Russo P, Foli A, et al. Salvage therapy with lenalidomide and dexamethasone in patients with advanced AL amyloidosis refractory to melphalan, bortezomib, and thalidomide. Ann Hematol; 91: 89-92.

[90] Palladini G, Russo P, Foli A, et al. Salvage therapy with lenalidomide and dexamethasone in patients with advanced AL amyloidosis refractory to melphalan, bortezomib, and thalidomide. Ann Hematol. 2012; 91: 89-92.

[91] Dispenzieri A, Lacy M, Zeldenrust S, et al .The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. Blood. 2007; 109: 465-470.

[92] Sanchorawala V, Wright D, Rosenzweig M, et al. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. Blood. 2007; 109: 492-496.

[93] Sanchorawala V, Finn KT, Fennessey S, et al. Durable hematologic complete responses can be achieved with lenalidomide in AL amyloidosis. Blood. 2010; 116: 1990-1991.

[94] Moreau P, Jaccard A, Benboubker L ,et al. Lenalidomide in combination with melphalan and dexamethasone in patients with newly-diagnosed AL amyloidosis: a multicenter phase 1/2 dose escalation study. Blood. 2010.

[95] Kastritis E, Roussou M, Migkou M, et al. A Phase I/II Study of Lenalidomide (R) with Low Dose Dexamethasone (d) and Cyclophosphamide (C) for Patients with Primary Systemic (AL) Amyloidosis. Blood. 2009: 177-178.

[96] Palladini G, Russo P, Bragotti L, et al. A Phase II Trial of Cyclophosphamide, Lenalidomide and Dexamethasone (CLD (in Previously Treated Patients with AL Amyloidosis. Blood. 2009: 1117-1118.

[97] Kumar S, Hayman S, Buadi F, et al. A Phase II Trial of Lenalidomide, Cyclophosphamide and Dexamethasone (RCD) in Patients with Light Chain Amyloidosis. Blood. 2009: 1482-1482.

[98] Kumar SK, Hayman SR, Buadi FK, et al. Lenalidomide, cyclophosphamide and dexamethasone (CRd) for light chain amyloidosis: long term results from a phase 2 trial. Blood.

[99] Kastritis E, Terpos E, Roussou M, et al. A phase I/II study of lenalidomide with low dose oral cyclophosphamide and low dose dexamethasone (RdC) in AL amyloidosis. Blood.

[100] Kastritis E, Terpos E, Roussou M, et al. A phase 1/2 study of lenalidomide with low-dose oral cyclophosphamide and low-dose dexamethasone (RdC) in AL amyloidosis. Blood. 2012; 119: 5384-5390.

[101] Kumar SK, Hayman SR, Buadi FK, et al. Lenalidomide, cyclophosphamide, and dexamethasone (CRd) for light-chain amyloidosis: long-term results from a phase 2 trial. Blood; 119: 4860-4867.

[102] Kumar SK, Hayman SR, Buadi FK, et al. Lenalidomide, cyclophosphamide, and dexamethasone (CRd) for light-chain amyloidosis: long-term results from a phase 2 trial. Blood. 2012; 119: 4860-4867.

[103] Palladini G, Russo P, Milani P, et al. A phase II trial of cyclophosphamide, lenalidomide and dexamethasone in previously treated patients with AL amyloidosis. Haematologica. 2012.

[104] Mahmood S, Venner CP, Sachchithanantham S, et al. Lenalidomide and dexamethasone for systemic AL amyloidosis following prior treatment with thalidomide or bortezomib regimens. Br J Haematol. 2014; 166: 842-848.

[105] Dispenzieri A, Buadi F, Laumann K, et al. The activity of pomalidomide in patients with immunoglobulin light chain amyloidosis. Blood. 2012.

[106] Specter R, Sanchorawala V, Seldin D, et al. Kidney dysfunction during lenalidomide treatment for AL amyloidosis. Nephrol Dial Transplant. 2010.

[107] Lichtman EI, Seldin DC, Shelton A, Sanchorawala V. Single agent lenalidomide three times a week induces hematologic responses in AL amyloidosis patients on dialysis. Am J Hematol. 2014; 89: 706-708.

[108] Gibbs S, De Cruz M, Sattianayagam P, et al. Transient Post Chemotherapy Rise in NT Pro-BNP in AL Amyloidosis : Implications for Organ Response Assessment. Blood. 2009: 712-712.

[109] Tapan U, Seldin DC, Finn KT, et al. Increases in B-type natriuretic peptide (BNP) during treatment with lenalidomide in AL amyloidosis. Blood. 2010; 116: 5071-5072.

[110] Dispenzieri A, Dingli D, Kumar S, et al. Discordance between serum cardiac biomarker and immunoglobulin-free light-chain response in patients with immunoglobulin light-chain amyloidosis treated with immune modulatory drugs. Am J Hematol. 2010; 85: 757-759.

[111] Dimopoulos MA, Richardson PG, Brandenburg N, et al. A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide. Blood. 2012; 119: 2764-2767.

[112] Sanchorawala V, Shelton AC, Zeldis JB, Seldin DC. Risk of second primary malignancy in patients with AL amyloidosis treated with lenalidomide. Am J Hematol. 2013.719 :88 ;

[113] Mitsiades CS, Davies FE, Laubach JP, et al. Future directions of next-generation novel therapies, combination approaches, and the development of personalized medicine in myeloma. J Clin Oncol. 2011; 29: 1916-1923.

[114] Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011; 364: 1046-1060.

[115] Oliva L, Pengo N, Palladini G, et al. Proteasome activity and stress in light chain amyloidosis. Amyloid. 2010; 17: 99.

[116] Reece D, Sanchorawala V, Hegenbart U, et al. Weekly and twice-weekly bortezomib in patients with systemic AL amyloidosis: results of a phase 1 dose-escalation study. Blood. 2009; 114: 1489-1497.

[117] Comenzo RL, Hegenbart U, Sanchorawala W, et al. High rates of overall and complete haematologic response in a prospective phase 1/2 study of weekly and twice weekly bortezomib in relapsed AL amyloidosis. Amyloid. 2010; 17: 83-84.

[118] Reece DE, Hegenbart U, Sanchorawala V, et al. Efficacy and safety of once-weekly and twice-weekly bortezomib in patients

with relapsed systemic AL amyloidosis: results of a phase 1/2 study. Blood. 2011; 118: 865-873.

[119] Reece DE, Hegenbart U, Sanchorawala V, et al. Long-term follow-up from a phase 1/2 study of single-agent bortezomib in relapsed systemic AL amyloidosis. Blood. 2014.

[120] Kastritis E, Anagnostopoulos A, Roussou M, et al. Treatment of light chain (AL) amyloidosis with the combination of bortezomib and dexamethasone. Haematologica. 2007; 92: 1351-1358.

[121] Wechalekar AD, Lachmann HJ, Goodman HJ, Bradwell A, Hawkins PN, Gillmore JD. AL amyloidosis associated with IgM paraproteinemia: clinical profile and treatment outcome. Blood. 2008; 112: 4009-4016.

[122] Kastritis E, Wechalekar A, Dimopoulos M, et al. Bortezomib with or without dexamethasone in primary systemic (light chain) amyloidosis. J Clin Oncol. 2010; 28: 1031-1037.

[123] Venner CP, Lane T, Foard D, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. Blood; 119: 4387-4390.

[124] Venner CP, Lane T, Foard D, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. Blood. 2012; 119: 4387-4390.

[125] Lacy MQ, Allred JB, Gertz MA ,et al. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease. Blood; 118: 2970-2975.

[126] Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood. 2012; 119: 4391-4394.

[127] Palladini G, Milani P, Foli A, et al. Treatment of AL Amyloidosis with Bortezomib Combined with Alkylating Agents: Results From a Prospective Series of Unselected Patients. ASH Annual Meeting Abstracts. 2011; 118: 3977.-

[128] Jaccard A, Comenzo RL, Hari P, et al. Efficacy of bortezomib, cyclophosphamide and dexamethasone in treatment-naive patients with high-risk cardiac AL amyloidosis (Mayo Clinic stage III). Haematologica. 2014; 99: 1479-1485.

[129] Palladini G, Milani P, Foli A, et al. Melphalan and dexamethasone with or without bortezomib in newly diagnosed AL amyloidosis: a matched case-control study on 174 patients. Leukemia. 2014.

[130] Enrico O, Gabriele B, Nadia C, et al. Unexpected cardiotoxicity in haematological bortezomib treated patients. Br J Haematol. 2007; 138: 396-397.

[131] Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol. 2011; 12: 431-440.

[132] Shah G, Kaul E, Fallo S, et al. Bortezomib subcutaneous injection in combination regimens for myeloma or systemic light-chain amyloidosis: a retrospective chart review of response rates and toxicity in newly diagnosed patients. Clin Ther. 2013; 35: 1614-1620.

[133] Landau H, Hassoun H, Bello C, et al. Adjuvant bortezomib and dexamethasone following risk-adapted melphalan and stem cell transplant in systemic AL amyloidosis. Amyloid. 2010; 17: 80.

[134] Sanchorawala V, Quillen K, Sloan JM, Andrea NT, Seldin DC. Bortezomib and high-dose melphalan conditioning for stem cell transplantation for AL amyloidosis: a pilot study. Haematologica. 2011; 96: 1890-1892.

[135] Kumar S, Gertz M, Lacy M, et al. Recent Improvements In Survival In Light Chain Amyloidosis and the Importance of An Early Mortality Risk Score. ASH Annual Meeting Abstracts; 116: 1892.

[136] Kumar S ,Gertz M, Lacy M, et al. Recent Improvements In Survival In Light Chain Amyloidosis and the Importance of An Early Mortality Risk Score. ASH Annual Meeting Abstracts. 2011; 116: 1892.

[137] Merlini G, Palladini G. Treating advanced cardiac damage in light chain amyloidosis: still an unmet need. Haematologica. 2014; 99: 1407-1409.

[138] Palladini G, Milani P, Foli A, et al. Oral melphalan and dexamethasone grants extended survival with minimal toxicity in AL amyloidosis: long-term results of a risk-adapted approach. Haematologica. 2014; 99: 743-750.

[139] Ludwig H, Durie BG, McCarthy P, et al. IMWG consensus on maintenance therapy in multiple myeloma. Blood. 2012; 119: 3003-3015.

[140] Wechalekar A, Merlini G, Gillmore JD, et al. Role of NT-ProBNP to Assess the Adequacy of Treatment Response in AL Amyloidosis. Blood. 2008; 112: 596-597.

[141] Venner CP, Gillmore JD, Sachchithanantham S, et al. Stringent patient selection improves outcomes in AL amyloidosis after autologous stem cell transplantation in the upfront and relapsed setting. Haematologica. 2014.

[142] Gertz MA, Dispenzieri A. Immunoglobulin light-chain amyloidosis: growing recognition, new approaches to therapy, active clinical trials. Oncology (Williston Park). 2012; 26: 152-161.

[143] Palladini G, Dispenzieri A ,Gertz MA, et al. New Criteria for Response to Treatment in Immunoglobulin Light Chain Amyloidosis Based on Free Light Chain Measurement and Cardiac Biomarkers: Impact on Survival Outcomes. J Clin Oncol. 2012.