

Systemic Amyloidosis Due to Low Grade Lymphoma

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Words:

Introduction

Lymphoma related AL amyloidosis (LR-AL) is a rare entity. Systemic AL amyloidosis is generally caused by an underlying plasma cell clone in the bone marrow (1) with an intact monoclonal IgG or IgA immunoglobulin protein identified 45-55% of cases. IgM light chain (AL) accounts for around 5-7% of all cases with systemic AL Amyloidosis and is typically associated with an underlying lymphoplasmacytic lymphoma. (2-5) Other low-grade non-Hodgkin's lymphomas are a rare cause of amyloidosis.

Lymphoma related AL amyloidosis (LR-AL) is a distinct clinical entity several distinguishing clinical features from AL amyloidosis in general.(6)(7) IgM related AL amyloidosis, the commonest LR-AL, follows systemic AL amyloidosis in general in terms of presentation. Other LR-AL presents with amyloid deposition at specific localised sites including the lacrimal gland, breast, lung, stomach and lymph nodes. These cases often lack a clearly detectable circulating monoclonal protein or abnormal serum free light chains. In general, the patients with IgM AL have a lower light chain burden, but also poorer hematologic response rates to treatment reflecting very often a more resistant underlying lymphoplasmacytic (LPL) clone. Those clones biologically behave similarly to Waldenstrom's disease, which is characterized by a slower progression and higher chemotherapy resistance. In comparison to non-IgM AL, fewer patients with IgM AL achieve a CR with a dFLC<10 mg/L or iFLC <20 mg/L.

AL amyloidosis is already a rare disease and LR-AL is rarer. The low patient number of the LR-AL/IgM AL subgroup makes the generation of data in randomized trials and the determination of the optimal treatment almost impossible. Therefore, treatment recommendations discussed here are based on either retrospective or small prospective trials of single centers. The treatment paradigms designed for non-IgM AL have been used in IgM

AL amyloidosis with limited efficacy and, regimens designed for low grade non-Hodgkin's lymphoma are needed to treat these cases.

Clinical Features of lymphoma related amyloidosis

Amyloidosis due to low grade lymphoma can be broadly classified into three main categories: IgM related AL amyloidosis, Sjogren's syndrome associated amyloidosis and localised lymphoma related AL amyloidosis. There can be a significant overlap between the latter two categories especially when the diagnosis of Sjogren's syndrome is not clear.

IgM related AL amyloidosis

Systemic AL amyloidosis with presence of an IgM monoclonal protein is the commonest type of lymphoma associated AL amyloidosis. This entity was originally described by the Mayo clinic group in a series of 50 patients with IgM gammopathy presenting with AL amyloidosis(3). The presentation was cardiac, renal, hepatic, and pulmonary amyloid seen in 44%, 32%, 14%, and 10% of patients, respectively. Despite this, the organ involvement in IgM-AL appears to be distinct with greater propensity for nerve, lymph node and lung involvement with less frequent cardiac involvement at presentation.(5, 7) A European collaborative series reported 250 patients with IgM-AL amyloidosis showing patients with IgM AL amyloidosis had a median IgM monoclonal paraprotein level of 10g/L, lower presenting serum free light chains (difference between the involved and uninvolved light chain >50mg/L in less than 2/3rd of all patients) and less frequent lambda light chain isotype (Figure 1a).(8) Cardiac involvement was less common in just under half of all patients with more frequent lymph node (20%) and neuropathic (28%) involvement compared with non-IgM AL. Cardiac involvement, advanced Mayo disease stage, neuropathic involvement, and liver involvement were independent factors that had an impact on survival. Sidana *et al.* from the Mayo Clinic provided a comprehensive evaluation of IgM AL patients' outcomes with either LPL or pure

plasma cell neoplasm (PPCNs) as an underlying clone. (9) They analyzed bone marrow biopsies of 70 IgM AL patients and found that 23% (16/70 patients) patients had a PPCN clone and 63% (44/70 patients) had an LPL clone which included a characteristic *LPL* in 39% (27/70) of patients and a low-grade B-cell lymphoma with plasmacytic differentiation, not further classifiable in 24% (17/70) of patients. In the remaining patients, no other diagnosis could be made, or there were too few cells.(9)

The prognosis of IgM related AL amyloidosis remains poorer than AL in general due to lack of treatments that can achieve deep clonal responses. (8) Cardiac involvement remains the major determinant of outcomes with worsening outcomes with progressive Mayo 2004 disease stage (Stage 1 – median 73 months vs. stage 2 – 24 months vs. stage 3 – 10 months). Overall survival was shorter in IgM AL compared to AL in general (when stratified by Mayo 2012 stage; stage 1/2 (59 vs. 125.9 months, $p = 0.003$) and stage 3/4 (6.5 vs. 12.9 months, $p = 0.075$) likely due to lower hematologic response rates (6 months: 39% vs. 59%, $p = 0.008$). Due to the unique characteristics of the disease, liver involvement and neuropathy are additional independent prognostic factors. Combining abnormal N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T with liver involvement and the presence of neuropathy gives IgM-AL specific risk stratification model: median OS of patients with none, one, or two or more abnormal factors was 90, 33, and 16 months, respectively (Figure 1b). (8)

Sjogren's syndrome related AL amyloidosis

The association of Sjogren's syndrome (SS) with low grade NHL is well recognised (10) with a 1000 fold higher incidence of marginal zone and MALT lymphomas. (11) Amyloidosis associated with Sjogren's syndrome has been frequently reported but data is limited to as individual case reports and very small retrospective series. The sites of amyloidosis track the common sites of lymphoma in SS and include skin, lung, breast, salivary

glands and vocal cords. Deposits can be seen at more than one site. The amyloid deposits are likely to be due to local production of amyloidogenic light chains by the MALT/marginal zone NHL. However, in a significant proportion of cases with amyloidosis in SS, the clonal infiltrate can be difficult to identify clearly due to the extensive amyloid infiltration dispersing the clonal lymphoid cells. The amyloid deposits in skin, breast and salivary glands usually present as localised nodular deposits or glandular enlargement, respectively. The breast deposits are often identified during screening for breast malignancies due to presence of breast nodules and can be bilateral.(12) Pulmonary amyloidosis is the most challenging of the manifestations as there is significant overlap with lymphoid interstitial pneumonitis (LIP). Patients may present with single or multiple lung nodules presenting as hemoptysis or progressive cough and shortness of breath. However, they can progress to interstitial amyloid deposition and cystic lung changes which can lead to irreversible debilitating pulmonary symptoms.(13) LIP is a close differential diagnosis and often difficult to differentiate.

The history of Sjogren's syndrome pre-dates the amyloid diagnosis variably between 1-20 years and majority of the patients have hypergammaglobulinemia and positive autoantibodies (Rheumatoid factor or anti-Ro/SSA or anti La/SSB antibodies). (14) Distinction between systemic AL amyloidosis causing sicca syndrome is important from the localised amyloidosis caused by Sjogren's syndrome. The localised amyloid deposits in Sjogren's syndrome rarely progress to systemic amyloidosis. SS is commoner in women and amyloidosis due to SS is also commoner in women. The localised amyloid deposits are always AL type. Rare patients with systemic AA amyloidosis have been described but they almost always have an overlap rheumatological disorder and present with renal involvement.

Other Lymphoma related amyloidosis

Amyloidosis due to lymphoma (other than IgM related AL and SS associated AL) is rare. Majority of such cases are localised amyloid deposits in the skin, conjunctiva, orbits, lung or lymph nodes commonly associated with marginal zone/MALT lymphoma.(15) The deposits are almost always at one single site (apart from lymph node amyloid deposits), rarely associated with circulation monoclonal protein, typically indolent or slowly progressive and very often do not require any systemic intervention.(16) Rare cases of systemic AL amyloidosis have been reported with chronic lymphocytic leukemia (17) and follicular lymphoma (18). In most cases of lymphoma associated amyloidosis, there is plasmacytic differentiation of the lymphoid malignancy. Wider use of MYD-88 testing as well as presence of IgH translocations may help to differentiate from LPL or true plasma cell clones.

Diagnostic work up for Lymphoma related AL amyloidosis

The diagnosis and assessments of lymphoma related AL remain similar to those with systemic AL amyloidosis in general. A tissue biopsy is required to confirm the diagnosis of amyloidosis followed by confirmation of amyloid fibril type. Confirmation of fibril type in IgM related AL amyloidosis appears be more challenging on immunohistochemistry and laser capture followed by mass spectrometry is often required for confirmation.(19, 20) Accurate identification of the underlying low grade NHL and its type is important to planning management. Detailed review of any biopsy material by a hematopathologist is crucial. Assessment of MYD-88 and IgH translocations on bone marrow samples is helpful to differentiate between LPL and neoplastic plasma cell clone. (21, 22)

Most patients with lymphoma related amyloidosis (especially patients with localised amyloid deposits) require whole-body cross-sectional imaging to identify lymph node enlargement and other disease sites which may impact management decisions. ¹⁸FDG-PET

scanning is useful in some cases to identify areas of amyloid deposition in patients with localised NHL related amyloidosis. (23) FDG uptake is typically low grade. The reason for FDG positivity is likely to be a combination of the local NHL clone or tissue macrophage reaction to amyloid deposits. (23) FGD-PET almost never show uptake in visceral organ affected by amyloid deposition. Newer PET tracers such as 18F-Florbetaben are interesting for systemic amyloid imaging (24) but await further evaluation. Cardiac evaluation by echocardiography including global 2-D strain measurements as well as cardiac magnetic resonance imaging is required at baseline. (25) Assessment of liver involvement including liver size by ultrasound or CT scanning, ¹²³I SAP scintigraphy (where available) and liver function tests is important. (26, 27) Factor X levels and clotting factor assessments are required based on presentation with bleeding symptoms.

Treatment for Lymphoma related-AL Amyloidosis

Lymphoma related AL patients are rarely treated with regimens that showed efficacy in the treatment of non-IgM AL amyloidosis. But given that the different underlying monoclonal clones consist in most cases of a lymphoplasmacytic lymphoma (LPL), regimens targeting Waldenstrom's disease should be considered. Furthermore, a better understanding of the role of genetic abnormalities such as CXCR4^{WHIM} or MYD88^{LL265P} mutations in the pathogenesis of IgM AL will help to better tailor treatments according to the underlying biology of the light chain producing clone.

Furthermore, the fact that patients with IgM AL do not respond well to a plasma cell-directed regimen is not a surprise as, in those cases, an NHL is treated with myeloma directed therapy. Based on the fundamental biological differences in patients with LR-AL versus PPCN IgM AL, patients should be treated according to their underlying clone to ensure a tailored

treatment for either an LPL or PPCN. Patients with Sjogren's syndrome related AL or other lymphoma related AL follow the paradigm described for the IgM related AL patients with caveat that non-progressive local lesions may not require chemotherapy treatment and individual lesions, at amenable sites, can be considered for treatment with local radiotherapy.

Treatment for IgM-AL Amyloidosis

There are no prospective randomized studies on IgM amyloidosis, and the published treatment regimens are very heterogeneous. In a large European collaborative study of patients with IgM related AL amyloidosis, 172 had available data on hematologic response. The hematologic response rate was 57% with 43% PR, 9% VGPR and 5% complete response (CR). The median OS was not reached for patients achieving VGPR/CR, 64 months for PR, and 28 months for non-responders ($P < .001$). Organ response rates were poor, with renal and cardiac response rates of 18% and 5%. (8)

A retrospective trial from the Boston Amyloidosis Center analyzed the treatment responses for 46 patients after 2003.(28) They chose the regimens based on the bone marrow pathology and patient-specific factors. The hematologic ORR and VGPR/CR were: high-dose melphalan/stem cell transplant (HDM/SCT) 100% and 80%, Bortezomib 82% and 27%, Rituximab 80% and 27%, immunomodulatory agents (IMiDs) 75% and 0%, and standard-dose alkylating agents (melphalan or cyclophosphamide) 63% and 19%. Overall, the 5-year survival rates were significantly higher in patients with a hematologic response: $79.2 \pm 8.5\%$ versus $41 \pm 14.9\%$ in non-responders, which is more favorable than typically expected in AL amyloidosis.(28)

Both retrospective studies from Amyloid centers reflect the relatively low rate of deep remission, translating into low organ responses and subsequent poorer outcomes.

ASCT

Although the role of ASCT in Waldenstrom is not well established and only recommended in selected cases, several studies have shown that ASCT is a very effective therapy for patients with IgM AL. In a retrospective analysis, Sidiqi et al. from the Mayo Clinic reported 38 patients receiving autologous stem cell transplant (ASCT) for IgM AL at the between May 1999 and June 2018.(2) The overall response rate (ORR) was 92%, and 76% of patients achieved at least a very good partial response (VGPR). The median overall survival was 106 months, and the PFS 48 months. Organ response predicted an improved PFS and OS (median PFS 93 months for organ response vs. 16 months for no organ response, $p=0.0006$ and median OS 123 months for organ response vs. 41 months for no organ response, $p=0.02$). The 100-day transplant-related mortality was low, with 5% (2 patients). The authors reported that the conditioning regimen has changed over time. Whereas the preferred regimen was High Dose melphalan in earlier years, in recent years, they have moved towards carmustine, etoposide, cytarabine, and melphalan (BEAM) conditioning in patients with the lymphoplasmacytic disease. Specifically, 84% ($n=32$) of patients received high dose melphalan ($200\text{mg}/\text{m}^2$ in 63% $n=24$ and $140\text{mg}/\text{m}^2$ in 21% $n=8$). Six patients received conditioning with BEAM. Patients did not receive maintenance. Renal responses were seen in 65% (15/23) (median time 18 months post ASCT, range 3-52 months), and cardiac responses in 60% (6/10) of patients (median time 12 months post ASCT, range 10-35 months).(2)

Those data are very encouraging, but unfortunately, despite the marked decrease in transplant-related mortality to around 5% and the fact that ASCT is an effective therapy in

patients with IgM related AL amyloidosis, only about 20% of patients might be eligible for this modality.

Rituximab based Regimens

Patients with IgM AL usually have a lower response compared to those with a non-IgM related disease. The biological features of the underlying neoplastic clone in patients with IgM related AL amyloidosis, especially with an LPL phenotype resembling low grade non-Hodgkin lymphoma requires a clone specific treatment, which was not always considered based on the heterogeneous data in the literature. In most of the IgM AL, an LPL clone is the underlying source of the production of FLC requiring regimen used in Waldenstrom's disease.

A small study of 10 patients treated with a combination of rituximab, bortezomib and dexamethasone showed a promising response rate in 7/9 (78%) patients, suggesting that CD20 directed therapy in conjunction with anti-plasma cell therapy is a very effective approach (29). Despite the very promising response rates, the use of bortezomib remains a challenge because of the high frequency of peripheral neuropathy in IgM amyloidosis.

In the large European trial, it was shown that since 2010, the use of rituximab in combination with bortezomib; cyclophosphamide and dexamethasone [R-CD]; rituximab plus cyclophosphamide, vincristine, and prednisolone [R-CVP]; or rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisolone [R-CHOP]) has increased. The rituximab-containing regimens resulted in PR or better responses in 63% of patients (8)

Bendamustine

Bendamustine is a bifunctional alkylating agent with efficacy in treating several hematologic malignancies, including chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and multiple myeloma. Bendamustine induces DNA interstrand crosslinks leading to cytotoxicity. (30, 31) Also bendamustine blocks several mitotic checkpoints, DNA repair and induces apoptosis via a p53-dependent DNA damage stress response (32) Based on the

encouraging data from using bendamustine in multiple myeloma, Lentzsch et al. performed a multicenter phase 2 clinical trial of bendamustine combined with dexamethasone for relapsed or refractory AL. This trial includes all subtypes of AL. 57% of patients achieved a PR or better (11% complete response, 18% very good partial response). The organ response was 29%. In this frail patient population, treatment with bendamustine was well tolerated with no grade 5 treatment-related adverse events. The median overall survival was 18.2 months (95% confidence interval (CI) 11.3-43.8 months), and the hematologic response was associated with significantly better survival ($p=0.0291$). (33) Based on the high response rates of bendamustine in multiple myeloma and bendamustine combined with rituximab (BR) in patients with low-grade lymphoma, BR has also been used for patients with IgM AL. Manwani et al. reported the outcomes in 27 patients treated with Bendamustine (90mg/m²) and rituximab (375mg/m²). (34). The ORR on an intention-to-treat (ITT) basis was 59%. Hematological responses were: complete response (CR) in 11% of patients, VGPR in 37%, partial response (PR) in 11%, and no response (NR) in 41% (including 22% deaths). Among the five patients treated for refractory AL, 3 achieved a VGPR, and 2 were non-responders (including one death). On a 6-month landmark analysis of patients who achieved VGPR or better, median OS and PFS were not reached, compared with 34 and 11 months, respectively, in patients who did not. Even though Manwani et al. presented a small retrospective study, the data demonstrate an excellent hematological response with 48% VGPR or better on an ITT basis. Even in a relapsed situation, 60% of patients treated with second-line BR achieved a VGPR.(34)

Those data suggest that upfront bendamustine in combination with rituximab leads to long-lasting and high response rates in IgM AL. The regimen is also well-tolerated, as Bendamustine has an excellent safety profile. It is neither neurotoxic nor cardiotoxic, and dosing is not affected by renal failure, suggesting that BR is an excellent choice for patients

with IgM AL. Based on the promising data, this combination should be further studied in larger prospective trials patients with IgM related AL amyloidosis.

Other Alkylating Agents

The Boston Amyloidosis Center reported a series of 27 patients treated with Melphalan or Cyclophosphamide. 63% of the patients achieved a PR with 19% CR/VGPR. (28) In a large European collaborative study of patients with IgM related AL, different combinations of cyclophosphamide in regimens such as CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisolone) and COP (cyclophosphamide, vincristine, and prednisolone) resulted in a PR rate of 62% but none achieved a VGPR or better **0% response** (8)

IMiDs

Despite the extensive use of Immunomodulatory Derivatives (IMiDs) such as thalidomide, lenalidomide and pomalidomide in multiple myeloma, only a few data on the efficacy of IMiDs in IgM AL are available. The European study reported **11 patients** treated with thalidomide resulting in a PR **or better in 63% and VGPR or better in 9% of patients**(8) The Boston Amyloidosis Center treated only four patients with IMiDs, three only achieving a partial response to therapy. (28) Based on those data and the lack of efficacy of IMiDs in WM, we cannot recommend IMiDs for LPL IgM AL. In patients with PPCN IgM AL, IMiDs might be considered if no other options are available. However, deep hematologic responses are not seen with IMiDs, which is critical for organ response and survival.

Ibrutinib

Bruton's tyrosine kinase (BTK) is a cytoplasmatic tyrosine kinase expressed in B-cells. The BTK inhibitor, ibrutinib, is approved for the treatment of several B cell malignancies including Waldenstrom's Macroglobulinemia. Treon et al., reported an impressive response

rate of 90.5% of patients with relapsed/refractory WM.(35, 36) Based on those data, Pika et al., from the Heidelberg Group in Germany retrospectively evaluated the effect of Ibrutinib therapy in 8 patients with AL associated with WM or marginal zone lymphoma.(37) The treatment did neither affect the free light chains nor the complete M-protein molecules in 5 patients, and one patient even had hematologic progression during the treatment. The therapy was not well tolerated and associated with multiple adverse events, including peripheral edema, especially in patients with cardiac and kidney involvement, and polyneuropathy. Two patients developed atrial fibrillation, and one patient with preexisting atrial fibrillation experienced a transient ischemic attack. The data suggested that although ibrutinib treatment is associated with a high percentage of therapeutic responses in WM, it is not recommended for IgM AL due to a considerable amount of adverse effects translating into poor survival in this small subgroup of pretreated systemic AL. (37)

Response Assessment and Goals of Treatment

We recommend evaluating hematologic response based on the consensus criteria for the difference in involved and uninvolved free light chains (dFLC) (38) For patients with a low free light chain burden $dFLC < 5$ mg/dL, the VGPR assessment with a $dFLC < 4$ cannot be used. The complete response (CR) assessment or decrease in dFLC to < 1 mg/dL should be used.(39-41) If present the baseline monoclonal protein of at least 0.5g/dL should be assessed by criteria for WM response (42) Both FLC and monoclonal protein should be included in the evaluation of the response as often only one parameter is elevated.

The goal of the treatment is to achieve the deepest response possible, as it was shown in a study by Sidana et al., that the FLC and M-spike CR lead to the best outcome. They showed that dFLC complete response resulted in a significantly longer OS (83.4 vs. 8.9 months, $p = 0.006$). Similarly, the achievement of monoclonal protein complete response led to a

significantly longer OS (83.4 months vs. 6.5 months, $p < 0.001$) (9) Nevertheless, it is known that the induction of hematologic CR associated with organ response is much more difficult to achieve in IgM AL than in non-IgM AL. Sidana et al reported significantly lower hematologic response rates in the IgM AL compared with non-IgM AL with an ORR of 39% vs. 59%, $p = 0.008$ and a CR/VGPR of 24% vs. 41%, $p = 0.02$ at 6 months. The poorer HRR resulted in lower organ response rates for heart, kidney, and liver in the IgM cohort, with response rates being 35% (6/17), 40% (10/25), and 0% (0/5), respectively compared to non-IgM AL organ responses (heart: 47%, kidney: 48%, and liver: 41%)(9)

Summary

LR-AL is rare but a distinct clinical entity. IgM related AL amyloidosis due to underlying LPL is the best studied, has systemic presentation and needs chemotherapy. A novel prognostic staging system has been described and should be used to risk stratify patients. Sjogren's syndrome related AL amyloidosis and other NHL related AL amyloidoses are typically localized diseases with amyloid deposition at one or more isolated site with rare progression to systemic disease. Treatment paradigm follows that for LPL or other low-grade NHL's with rituximab-based regimes. Despite new and improved treatment options, patients with IgM AL have a lower hematologic response to treatment resulting in an inferior outcome compared to patients with non-IgM AL. To tailor the treatment according to the underlying pathology and avoid treatment of LPL IgM AL with an anti-plasma cell-directed therapy, the determination of the underlying pathology LPL versus PPCN is of utmost importance.

Once the exact amyloid producing clone has been identified, therapy needs to target the deepest possible remission. Therefore, patients with an LPL morphology should receive an anti-CD20 directed treatment, such as rituximab combined with an alkylating agent such as Bendamustine, and bortezomib to target both the lymphoid and plasmacytic components of the

disease. This recommendation is mainly based on the observation that PR rates of 78% have been observed when IgM AL patients were treated with rituximab, bortezomib, and dexamethasone and that the combination of rituximab with bendamustine resulted in PR of 59% with impressive CR/VGPP rate of 48%(29, 34). This recommendation is further supported by the results of a phase II studies with rituximab, bendamustine, and bortezomib in low-grade B-cell lymphomas. The trials included lymphoplasmacytic and mantle cell lymphoma and resulted in high ORRs of 88– 94%, including CR rates of 53– 64%(43, 44). Nevertheless, we want to point out that no data investigating this regimen in IgM AL are available. Future trials are needed to support a regimen of Rituximab, Bendamustine, Bortezomib, and dexamethasone for IgM AL. Patient presenting with a neuropathic phenotype should avoid bortezomib.

In patients with a PPCN morphology, are best treated with a plasma cell directed treatment regime. We recommend treatment with daratumumab, cyclophosphamide, bortezomib and dexamethasone given an outstanding overall response rate of 96% with CR 54%, VGPR 82% in the run-in safety trial of 28 patients. The high hematologic response rates resulted in impressive organ response: 53% cardiac, 83 renal and 50 % liver response(45)

In contrast to Waldenstrom's disease, in which ASCT plays a minor role, ASCT in IgM AL amyloidosis has led to deep and durable response rates. Based on the Boston Amyloidosis Center and the Mayo Clinic's excellent data, reporting an ORR of 100% and 92%, respectively, ASCT needs to be considered in this patient population(9, 28). Unfortunately, only a small fraction of around 20 % of IgM AL might be eligible for ASCT. When considering ASCT, the conditioning regimens in patients with LPL morphology should be similar to those used for WM, such as BEAM and in patients PPCN morphology similar to myeloma such as melphalan. Treatment should be continued until the deepest remission is achieved. No data are supporting the role of maintenance in IgM AL.

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Take-home points

- Lymphoma related AL amyloidosis should be considered in any patient with systemic AL amyloidosis and IgM monoclonal protein, localized amyloid deposits, or underlying history of Sjogren's syndrome
- Bone marrow (or tissue biopsy) should be assessed for underlying lymphoproliferative disorder including MYD-88 testing.
- The goal of treatment is the induction of deepest remission (CR/VGPR) which translate into longer OS and better organ response
- Determine the underlying pathology to choose the optimal treatment
 - LPL: Rituxan, Bendamustine, Velcade, dexamethasone
 - PPCN: Dara-CYBORD
- Induction followed by ASCT achieves best results
- Consider always ASCT, as this translates in high hematologic and organ response rates
- Condition regimen for ASCT should be selected based on pathology
 - LPL: BEAM
 - PPCN: Melphalan
- Role of Maintenance is unclear.

Figure 1: 1a. Monoclonal IgM component and serum free light chains at presentation in IgM AL amyloidosis(5) 1b. Staging system for IgM AL amyloidosis using abnormal NTproBNP, abnormal troponin-T, liver involvement and neuropathy: stage 1 – one present, stage 2 – two present, stage 3 – three or more present (8)

Figure 2: Left two panels shows uptake in lymph nodes using ¹⁸F-Florbetaben in a patient with IgM related AL amyloidosis and marked lymphadenopathy on background of Waldenstrom's Macroglobulinemia. The right two panels show corresponding areas of uptake on FDG-PET for comparison. (24)

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Figure 1a

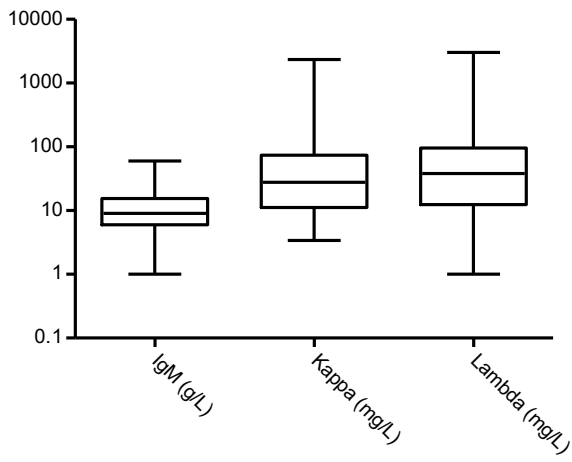


Figure 1b

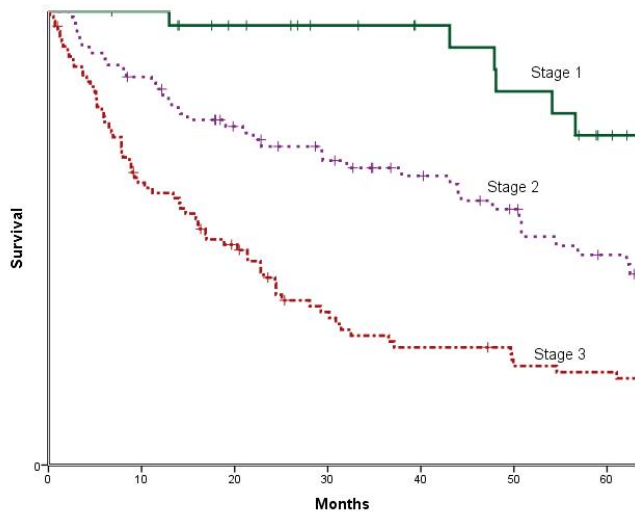


Figure 2

