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How I Treat AL Amyloidosis

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Abstract:
The treatment of patients with systemic light chain (AL) amyloidosis is a challenge to hematologists. Despite its generally small size, the underlying clone causes a rapidly progressing, often devastating multiorgan dysfunction through the toxic light chains that form amyloid deposits. Clinical manifestations are deceitful and too often recognized at an irreversible stage. However, hematologists are in the unique position to diagnose AL amyloidosis at a pre-symptomatic stage checking biomarkers of amyloid organ involvement in patients with monoclonal gammopathies at higher risk to develop the disease. Adequate technology and expertise are needed for a prompt and correct diagnosis, particularly for ruling out non-AL amyloidoses that are now also treatable. Therapy should be carefully tailored based on severity of organ involvement and clonal characteristics, and early and continual monitoring of response is critical. Three recent randomized clinical trials moved AL amyloidosis to evidence-based era. Above all, the daratumumab-bortezomib combination is a new standard-of-care for newly diagnosed patients inducing rapid and deep responses that translate into high rates of organ response. The availability of new effective drugs allows to better personalize the therapy, reduce toxicity, and improve outcomes. Patients should be treated within clinical trials whenever possible.

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How I treat AL amyloidosis

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Abstract

The treatment of patients with systemic light chain (AL) amyloidosis is a challenge to hematologists. Despite its generally small size, the underlying clone causes a rapidly progressing, often devastating multiorgan dysfunction through the toxic light chains that form amyloid deposits. Clinical manifestations are deceitful and too often recognized at an irreversible stage. However, hematologists are in the unique position to diagnose AL amyloidosis at a pre-symptomatic stage checking biomarkers of amyloid organ involvement in patients with monoclonal gammopathies at higher risk to develop the disease. Adequate technology and expertise are needed for a prompt and correct diagnosis, particularly for ruling out non-AL amyloidoses that are now also treatable. Therapy should be carefully tailored based on severity of organ involvement and clonal characteristics, and early and continual monitoring of response is critical. Three recent randomized clinical trials moved AL amyloidosis to evidence-based era. Above all, the daratumumab-bortezomib combination is a new standard-of-care for newly diagnosed patients inducing rapid and deep responses that translate into high rates of organ response. The availability of new effective drugs allows to better personalize the therapy, reduce toxicity, and improve outcomes. Patients should be treated within clinical trials whenever possible.

Introduction

Systemic immunoglobulin light chain (AL) amyloidosis is caused by the conversion of light chains (LCs) from their soluble states into highly-organized fibrillar aggregates that deposit in tissues, resulting in progressive organ damage and dysfunction.[1] Rapid organ deterioration imposes early diagnosis and prompt, effective therapies to halt disease progression and, possibly, rescue organ function.[2] Light chains, LC aggregates, or preceding intermediaries, may induce proteotoxicity leading to cell dysfunction and death, as shown in cardiac cells.[3-5] Cardiomyocytes, in response, produce high levels of natriuretic peptide type-B and its N-terminal fragment (BNP and NT-proBNP) that are pivotal for patient management.[6] Furthermore, amyloid fibrils may cause cell damage and distortion of tissue architecture contributing to organ dysfunction.[7] Accordingly, while experimental strategies aiming at reducing amyloid load are being developed, current therapy aims at suppressing the synthesis of the amyloid protein while adapting to patient's frailty.

Structural features of LCs underlie their amyloidogenicity. Approximately 80% are of lambda isotype, and a limited pool of LC variable region genotypes are responsible for the production of amyloidogenic free light chains (FLC), consistent with a biased selection.[8-11] Specific LC germline usage can partly explain organ tropism.[11,12] Somatic mutations, acquired during clonal selection, determine LC higher flexibility, kinetic instability, and a higher dynamic state that underlie amyloidogenicity and tissue toxicity. [13-16] Studies are ongoing to develop LC stabilizers expected to inhibit fibril formation and proteotoxicity.[17,18] N-glycosylation of kappa LCs is more common in patients with AL amyloidosis than in those with monoclonal gammopathy of undetermined significance (MGUS) or multiple myeloma (MM) and can be readily detected in serum by mass spectrometry.[19,20] These genetic and post-translational characteristics may be exploited, possibly through machine learning,[21] for detecting patients with plasma cell (PC) dyscrasias at high risk for developing AL amyloidosis, facilitating early diagnosis.[22]

Several studies have delineated the biologic characteristics of the B cell/PC clone that is usually small and indolent.[23] Amyloidogenic PCs are vulnerable to proteasome inhibitors, accounting for improved clinical outcomes after the introduction of bortezomib.[24,25]

Cytogenetic abnormalities are detected in approximately 80% of patients via fluorescent in situ hybridization (FISH). Translocation(11;14), is the most frequent (40% to 60% of patients), and is associated with poorer hematologic response rates and overall survival with bortezomib and dexamethasone with or without cyclophosphamide.[26] The BCL-2 inhibitor venetoclax is very effective in patients with t(11;14),[27] and larger, controlled studies of this agent are warranted. Gain(1q21) is present in 15%–20% of patients and is associated with poor response to oral melphalan.[28] Compared with MGUS/MM, AL amyloidosis shows less intra-clonal heterogeneity[29] and different transcriptional programs,[30] suggesting that AL amyloidosis may be more amenable to eradication than MM.

Case 1: a young, asymptomatic man with MGUS and increased cardiac biomarkers.

A 58-year-old, very active, man with low-intermediate risk IgG lambda MGUS diagnosed one year earlier, presented at the second yearly control with normal hematology and biochemistry values. Serum monoclonal spike was stable (8 g/L), as well as FLC concentration (lambda 180 mg/L, kappa 20 mg/L, ratio 0.11), proteinuria was 220 mg/d with urine immunofixation electrophoresis showing monoclonal lambda FLC. Bone marrow biopsy showed 8% lambda typic plasma cells, and FISH analysis disclosed t(11;14) in 35% of interphases. The patient was asymptomatic and working full time. The finding of a significant increase of NT-proBNP to 745 ng/L from the previous 114 ng/L raised the suspicion of heart involvement and an appropriate workup was started. The abdominal fat aspirate showed amyloid deposits that were typed as AL lambda by mass spectrometry. Echocardiography was normal. Cardiac magnetic resonance was consistent with early cardiac amyloidosis. Cardiac troponin I was 0.01 ng/mL, and the patient was classified cardiac stage[31] II. We thoroughly discussed the opportunity to start anti-clone therapy, carefully considering toxicity and benefit balance. The patient decided to start therapy and since he was eligible for autologous stem cell transplantation (ASCT), we started treatment with cyclophosphamide, bortezomib, and dexamethasone (CyBorD). During the first course, asymptomatic orthostatic hypotension (80/50 mmHg) occurred that resolved spontaneously. After 4 courses, a very good partial (VGPR) response was achieved

[lambda 48 mg/L, kappa 17 mg/L, difference between involved and uninvolved FLC (dFLC) 31 mg/L, positive serum and urine immunofixation]. Hemopoietic stem cells were harvested uneventfully. However, 3 months later, NT-proBNP increased to 954 ng/L and the patient reported unusual fatigue after strenuous physical exercise, while maintaining VGPR. The patient consented to proceed to high dose melphalan (200 mg/m^2). The procedure was uneventful. Three months after ASCT, he achieved complete hematologic response (CR), with reduction of NT-proBNP to 584 ng/L, thus qualifying for cardiac response. Eighteen months after ASCT, the patient is in CR, with negative minimal residual disease (MRD) by next generation flow cytometry, and NT-proBNP is now 98 ng/L.

Comments about patient 1

This patient illustrates the possibility to diagnose AL amyloidosis at a very early, asymptomatic, stage and to fully exploit the therapeutic armamentarium and restore organ function. About 3% to 5% of patients with a known precursor PC disorder will progress to AL amyloidosis. However, even in referral centers, it takes a median time of almost one year to reach the diagnosis, based on signs or symptoms, in patients with preexisting PC dyscrasias.[32] When symptoms manifest, even a minor delay translates into significant shortening of survival.[33] For this reason, we advocated the use of sensitive markers of amyloid organ involvement during the follow-up of individuals with MGUS to facilitate a pre-symptomatic diagnosis.[34] In this patient, an increase of NT-proBNP raised suspicion of amyloid cardiac involvement. NT-proBNP is a very sensitive marker, but it is not specific being elevated in other conditions, and heart involvement can be confirmed by echocardiography or magnetic resonance. Our diagnostic approach is reported in Figure 1. Once diagnosis is established, it is necessary to assess the risk to carefully balance expected benefit and possible treatment toxicity. Cardiac involvement is the main determinant of frailty and survival. Current validated staging systems are reported in Figure 2.[31,35-39] The patient was cardiac stage II and considering the young age and the perfect fit, he was eligible for high-dose melphalan and ASCT. Eligibility criteria vary for centers (Figure 3); however, only ~20% of newly diagnosed patients are eligible for this intensive treatment. ASCT is safe, with <3% treatment-related mortality in referral centers, and highly effective, providing ≥VGPR in approximately 70% of patients and a median

survival >15 years in patients achieving CR.[40,41] Induction therapy with bortezomib-based regimens should be considered in all transplant-eligible patients.[42,43] Furthermore, the recently concluded Andromeda trial, reported an unprecedented high rate of deep hematological responses (≥VGPR in 78.5%) for daratumumab plus CyBorD, which was recently approved by FDA and EMA for newly diagnosed AL amyloidosis.[44] Daratumumab-CyBorD is a new standard of care and will become also the preferred induction therapy before ASCT. Importantly, daratumumab-CyBorD is effective also in patients whose amyloid clones harbor the t(11;14) who have poorer outcomes with CyBorD alone.[44] Since daratumumab was not available in Italy at the time this patient was seen, he received CyBorD achieving VGPR after 4 courses. Based on data suggesting that ASCT can be deferred to relapse after successful induction, without detrimental effects on overall survival, we elected to postpone ASCT.[45-47] This practice is common in Europe. Actually, in a survey including 3064 patients treated between 2011 and 2018 in 10 European referral centers, ASCT was used frontline in 6% of patients, and as second line in 10%.[48] While some centers prefer to transplant all eligible patients upfront, we generally prefer to defer ASCT in subjects who attain CR and/or organ response after induction. However, at our center we proceed to ASCT in patients with multiple myeloma. In this patient, the appearance of mild symptoms and increase in NT-proBNP suggested that attaining VGPR was not sufficient to halt disease progression, and the patient proceeded to ASCT. Approximately 30% of patients do not respond to first line treatment and they should promptly switch to another class of drugs. Quality of organ response is strictly dependent on the depth of hematology response, and although in some patients VGPR or even PR is enough to reach it, in patients with highly toxic light chains, persistence of even MRD may be sufficient to hamper amelioration of organ function.[49] In patients who achieve CR without organ response, MRD evaluation may help decide regarding further therapy. Proposed criteria for grading organ response are now being validated.[50] The criteria for hematologic and organ response are reported in Table 1.[39,51-54] In this fit patient, stem cell collection was uneventful, although the incidence of major complications (hypotension, hypoxia, cardiac arrhythmia, and fluid retention), during stem cell mobilization and collection is approximately 15%. The patient was eligible for full dose melphalan (200 mg/m^2), which is important to optimize outcomes, and reached CR and cardiac response.

Case 2: a woman with rapidly worsening dyspnea and peripheral edema.

A 58-year-old woman began to experience exertional dyspnea. Three months later she was hospitalized because worsening dyspnea and pleural effusion. Echocardiogram reported left ventricular hypertrophy with preserved ejection fraction (55%). Diuresis resolved pleural effusion, and she was discharged. Over the next 6 months, symptoms worsened, and cardiac catheterization showed normal coronaries. Two months later the patient was seen in another cardiology center due to recurrent cardiac syncope and non-sustained ventricular tachycardia. An implantable cardioverter defibrillator (ICD) was implanted, and oral amiodarone was started. Echocardiography showed diastolic dysfunction and increased wall thickness (posterior wall 16 mm, interventricular septum 15 mm) with reduced ejection fraction (43%). The suspicion of cardiac amyloidosis was raised, and a scintigraphy with ^{99m}Tc-DPD and an endomyocardial biopsy were performed. The scintigraphy showed no cardiac uptake and the biopsy showed amyloid deposits, that were not further characterized. NT-proBNP was 10,740 ng/L, and troponin I 0.44 ng/mL. The patient was referred to our center two months later, more than one year after the onset of symptoms. She reported fatigue, dyspnea for minor exertion, petechiae and ecchymoses in the upper part of the body. Physical examination revealed mild macroglossia, jugular vein distention, pleural effusion, hepatomegaly, distal edema, and hypotension (86/53 mmHg). Serum and urine electrophoresis and immunofixation revealed an IgG kappa spike (28 g/L) with free kappa LCs, and Bence Jones proteinuria. Serum kappa FLC were 303 mg/L, (ratio 25.2, dFLC 291 mg/L). Bone marrow biopsy reported 31% monotypic kappa PC with gain1q21, and amyloid deposits. No other myeloma-defining events were present. Abdominal fat aspirate was positive for amyloid that was typed as AL kappa by immuno-electron microscopy. NT-proBNP was 15,585 ng/L and troponin I 0.53 ng/mL, echocardiography confirmed advanced amyloid involvement. The patient was stage IIIb, and since there was no sign of other organ damage, we started evaluation for cardiac transplantation. In the meantime, she started treatment with CyBorD with reduced bortezomib (1 mg/m^2), and dexamethasone (20 mg) dosage. After the second cycle she experienced worsening of heart failure that required hospitalization. Investigations revealed reduction of the serum monoclonal component to 19 g/L, and of dFLC 35 mg/L, qualifying for VGPR, while NT-proBNP increased to 16,834 ng/L and troponin I to 0.63 ng/L. Three days after admission the patient collapsed and died with pulseless electrical activity.

Comments about patient 2

This case illustrates the devastating effects of delayed diagnosis: in this rapidly progressing disease, “time is life” and even few months can irreversibly compromise any chance to benefit from effective therapies. Symptoms that should trigger an appropriate workup for amyloidosis are listed in Table 2. The diagnosis of cardiac amyloidosis can be augmented by machine learning applied to electrocardiographic and echocardiographic data.[55] In the European survey, the percentage of patients presenting with very advanced cardiac damage (stage IIIb) remained the same (15-16%), and median survival remained disappointingly low (4.5 months) in the periods 2004-2010 and 2011-2018.[56] A recent survey among US community and academic hematologists showed that low disease awareness, inadequate referral practices and screening/testing procedures account for 1-1.5 year diagnostic delay.[57] Scintigraphy with bone tracers (PYP or DPD) is used to search for cardiac transthyretin amyloidosis that usually shows strong uptake.[58] However, the presence of the monoclonal protein should be ascertained first, using appropriate methods (see figure 1), because its presence makes cardiac biopsy mandatory and scintigraphy unnecessary. In this case, the cardiologists elected to perform scintigraphy and cardiac biopsy concomitantly. Due to recurrent syncope and registered ventricular arrhythmias, an ICD was implanted. Probably, patients with very advanced cardiac amyloidosis [New York Heart Association (NYHA) class 4 and NT-proBNP >8500 ng/L and systolic blood pressure <90 mm of Hg] are not appropriate candidates for ICD implantation.[59] The patient reported recurrent purpura, a common finding particularly in advanced stages of the disease, that is attributed to amyloid infiltration of blood vessels. Coagulation abnormalities are multifactorial, including factor X and other factors deficiency, and occur in a significant proportion of patients.[60] These extremely fragile patients are very sensitive to treatment toxicity, and we attenuated treatment dosages. Although early and deep response is associated with improved survival in stage IIIb patients,[61] in this subject cardiac involvement was likely already too advanced. At present, there is no treatment capable of improving the outcome of most stage IIIb patients. However, subcutaneous daratumumab can induce rapid and deep responses, which makes it a valuable option also in these patients. A multicenter phase II trial of single-agent daratumumab in stage IIIb subjects is underway (NCT04131309). Moreover, removing amyloid deposits with antibodies is expected to improve outcomes and is currently being tested in clinical trials (Table 3). Young, stage IIIb patients with isolated heart involvement should be considered for cardiac

transplantation that is now associated with outcomes comparable to non-amyloid cardiomyopathy.[62] However, scarcity of donors frequently renders time on waiting list incompatible with patient's needs.

Case 3: a man with rheumatoid arthritis, proteinuria, smoldering MM, and bilateral carpal tunnel syndrome.

A 70-year-old man with a 1-year history of rheumatoid arthritis treated with hydroxychloroquine and prednisone (2.5 mg/d) and of smoldering multiple myeloma [IgG lambda, FLC ratio 0.08, dFLC 141 mg/L, bone marrow PC infiltrate 25% with t(11;14) in 25% of interphases] was referred to our center due to bilateral carpal tunnel syndrome and proteinuria 1.2 g/d (creatinine 0.71 mg/dL). There was no sign of amyloid cardiac involvement (normal echocardiography, NT-proBNP 42 ng/L, troponin I 0.03 ng/mL). Serum amyloid A apolipoprotein (SAA) level was normal. Abdominal fat aspirate was positive, and the amyloid deposits reacted with anti-lambda (and not with anti-SAA and anti-TTR) antibodies at immuno-electron microscopy. A diagnosis of AL amyloidosis with renal and soft tissue involvement was made, and the patient was enrolled in the ANDROMEDA trial and randomized to the daratumumab-CyBorD arm. After two infusions, treatment was interrupted due to a respiratory infection. However, by then, a VGPR had been reached (dFLC 13 mg/L, FLCR 0.61, positive serum immunofixation) with renal response (proteinuria 0.5 g/d). Cycle 2 was also interrupted after the second infusion due to a respiratory infection. The following four cycles were completed without complications, but we elected to withhold daratumumab maintenance. The patient is currently asymptomatic 2 years after treatment discontinuation and VGPR is maintained (dFLC 14 mg/L, FLCR 0.81, positive serum immunofixation).

Comments on patient 3

In this patient symptoms were recognized early, and the diagnosis was made when he was still renal stage I. However, this subject had a chronic inflammation (rheumatoid arthritis) that can give rise to AA (reactive) amyloidosis. Amyloidosis reactive to chronic

phlogosis is caused by deposition of SAA-derived amyloid fibrils and presents with renal damage.[63] Treatment is aimed at controlling the underlying inflammation. Moreover, carpal tunnel syndrome can be found both in AL and in transthyretin amyloidosis. Thus, accurate tissue typing was mandatory.

In this patient, bone marrow PC infiltrate was higher than 20%. This measure of clonal bulk is an additional negative prognostic factor independent of cardiac involvement,[64] as well as dFLC level.[37,53,54] The patient could be treated with daratumumab-CyBorD in the ANDROMEDA trial. This regimen is well tolerated, but one of the most common adverse events with daratumumab in AL amyloidosis is respiratory infection,[65] as occurred in this subject who was also immunocompromised by steroid treatment for rheumatoid arthritis. Nevertheless, the infection was manageable, and VGPR was reached after only 2 infusions. Prophylaxis of infections may be useful in patients with AL amyloidosis treated with daratumumab as was shown in multiple myeloma.[66] Besides its high efficacy, the ability of daratumumab to induce deep responses after the first infusion[67,68] is particularly relevant in patients with AL amyloidosis who need to reach a deep reduction of the amyloid LCs as soon as possible.

The role of maintenance has not been adequately explored in patients with AL amyloidosis. In the ANDROMEDA study, treatment with daratumumab could be continued for up to 2 years if well tolerated, but there was no control arm for maintenance. In our patient, who was prone to infections, we elected to withhold maintenance. Controlled studies are warranted to ascertain whether maintenance has a role in AL amyloidosis. At our center and at the Mayo Clinic,[69] maintenance is considered in patients with large clones (for instance fulfilling the SLiM CRAB criteria) and/or high-risk cytogenetics.

Case 4: an elderly man with macroglossia, peripheral edema and dysautonomia

A 72-year-old man developed worsening speech difficulty due to slowly progressing macroglossia. After 18 months, foamy urine, peripheral edema, impotence, and symptomatic postural hypotension with occasional syncope ensued and the patient sought medical advice. Proteinuria was present and the general practitioner suspected

amyloidosis and referred the patient to our center. He presented with typical macroglossia and submandibular gland swelling, nephrotic syndrome (proteinuria 5.9 g/d, normal creatinine), symptomatic orthostatic hypotension and hepatomegaly (8 cm below costal margin). Echocardiography revealed amyloid heart involvement, NT-proBNP was 5500 ng/L, and cardiac troponin I 0.05 ng/L. Alkaline phosphatase was elevated (480 U/L, upper reference limit 150 U/L) with normal bilirubin and aminotransferases. Immunofixation electrophoresis showed monoclonal lambda free light chains in serum and urine, circulating lambda FLC concentration was 849 mg/L (ratio 85, dFLC 840 mg/L). Bone marrow plasma cell infiltrate was 16%, with no chromosomal abnormalities by iFISH. Abdominal fat aspirate showed amyloid deposits characterized as AL-lambda type by immuno-electron microscopy. A diagnosis of AL amyloidosis with cardiac, renal, liver, soft tissue, and autonomic nervous system involvement was made, and the patient was enrolled in a clinical trial comparing melphalan and dexamethasone (MDex) with MDex plus bortezomib (BMDex). The patient was randomized to the BMDex arm. The use of fitted elastic leotards was recommended. Diuretic therapy was initiated before chemotherapy with furosemide 25 mg/d and the patient lost 2 Kg in one week. Higher doses of furosemide were not tolerated due to worsening hypotension. During the first BMDex course fluid retention worsened again. By the end of cycle 1, fluid retention and hypotension resolved and did not recur during subsequent cycles. After 3 cycles a PR was reached, and VGPR was attained after 6 cycles and maintained at the completion of cycle 8 (positive urine immunofixation, dFLC 33 mg/L, ratio 0.30), with cardiac (NT-proBNP 686 ng/L), renal (proteinuria 1.4 g/d), and liver (alkaline phosphatase 150 U/L) response, and treatment was discontinued. The patient was followed every 6 months for 5 years, when an increase in dFLC was observed (141 mg/L, ratio 0.06) with stable NT-proBNP (767 ng/L) and proteinuria (1.6 g/d). The only symptoms were mild fatigue and persistent involvement of soft tissues. Rescue treatment with ixazomib, lenalidomide and dexamethasone was started. After 2 cycles partial hematologic response was achieved (dFLC 61 mg/L, ratio 0.16) with stable symptoms, increased NT-proBNP (3835 ng/L), stable proteinuria (1.4 g/d), and an increase in serum creatinine (from 0.77 to 1.4 mg/dL). Treatment was continued for 4 more cycles with stable hematologic and organ parameters. After lenalidomide discontinuation, NT-proBNP level decreased to 480 ng/L.

Eighteen months later a new rise in dFLC was documented (169 mg/L, ratio 0.09) that was associated with stable NT-proBNP (576 ng/L), proteinuria (1.5 g/d), and creatinine (1.5 mg/dL). Rescue treatment with pomalidomide and dexamethasone was started. A VGPR was re-established after three cycles (dFLC 21 mg/L, ratio 0.48, persistent positive urine immunofixation). A probably pomalidomide-related increase in NT-proBNP was observed during therapy (up to 3057 ng/L) while renal involvement remained stable (proteinuria 1.3 g/d, creatinine 1.3 mg/dL). The patient is now 81-year-old, and he is enjoying an active life despite persistent macroglossia, with resolution of symptoms of heart and renal involvement and of hypotension.

Comments on patient 4

Symptoms of AL amyloidosis depend on organ involvement and can be often mistaken for manifestations of more common diseases. However, typical soft tissue involvement, and combination of signs of simultaneous involvement of different organs can be a clue to diagnosis as in this patient. Yet, multiorgan involvement makes these patients frail and difficult to treat intensively. Supportive measures to manage fluid retention, hypotension and malnutrition should be started early, possibly before initiation of chemotherapy (Table 3).[70] Dexamethasone can exacerbate fluid retention and arrhythmias and should be used at lower dosage (20 mg or less) in patients with advanced heart involvement (NYHA class III or IV, cardiac stage IIIb, repetitive ventricular arrhythmias).[71] At diagnosis, this patient was cardiac stage II and renal stage II, and he was not a candidate for stem cell transplantation due to age, heart involvement, and hypotension, qualifying as intermediate-risk. Bortezomib is the most used agent in upfront therapy, based on retrospective, uncontrolled studies.[35,72] Running controlled clinical trials has been difficult in AL amyloidosis, due to the relative rarity of this condition and the easy access to drugs licensed for multiple myeloma. This patient was enrolled in the AC-004-EU/EMN-03 trial comparing MDex and BMDex (NCT01277016). This academic, investigator-initiated study showed that BMDex grants higher hematologic response rates than MDex (81% vs. 57%, VGPR/CR 64% vs. 39%) and was the only study to demonstrate an overall survival advantage for the experimental arm in AL amyloidosis.[73] BMDex is well tolerated and

relatively inexpensive. Moreover, it can potentially overcome the effect of the two most common chromosomal abnormalities found in this disease, t(11;14) and gain 1q(21).[26,28] In this patient, BMDex induced VGPR with cardiac, renal, and liver response that lasted 5 years. It has recently been shown that restaging discriminates survival even after upfront therapy.[74] The patient had asymptomatic hematologic relapse and was rescued when he still was cardiac stage II. There are no validated criteria for hematologic progression in AL amyloidosis, and there is disagreement on when treatment should be started at relapse.[75-77] This is relevant not only for individual patients management, but also for the lack of validated definition of progression free survival in clinical trials. However, it is generally agreed that organ progression should not be awaited, because this is associated with shorter survival and time to dialysis.[39,51] Indeed, it is common practice at different referral centers to start treatment when early, relatively small increases in FLC (approximately 40% of baseline value) are detected.[78,79] Small increases in FLC should be regarded cautiously particularly in patients who presented with advanced cardiac involvement. Rescue therapy is discussed in Figure 4.This patient was rescued with a combination of ixazomib and lenalidomide,[80] and pomalidomide at first and second relapse, before progression became symptomatic. Although he never reached CR, his disease was controlled for ten years, with a good quality of life.

The optimal goal of therapy is yet to be established, and possibly varies during follow-up. In patients with this rapidly progressing disease, it is necessary to closely monitor (every 2 cycles), the outcome of therapy to promptly switch regimen and avoid further organ deterioration.[61,81] A deep reduction of FLC should be achieved very early,[81] but ideal timing and depth vary based on disease severity and treatment regimen. With daratumumab FLC usually drop after the first administration.[67] In patients with advanced cardiac involvement an earlier (after 1 cycle) assessment of response is advisable to allow a rapid shift in non-responders. This can be particularly relevant in subjects receiving daratumumab. At the end of frontline therapy either CR or organ response should be reached, and the recently validated composite hematologic and organ response criteria can offer guidance in this assessment.[82] However, in patients with an aggressive underlying clone (e.g., with SLiM CRAB or high-risk myeloma cytogenetics) CR might be more obstinately pursued, as recently suggested by the Mayo Clinic group.[69] In the longer

term, biomarkers of organ involvement should progressively decrease and normalize, indicating amyloid FLC concentration is kept at a level that does not prevent recovery of organ dysfunction.[50] In fit patients who fail to attain organ response despite CR, MRD assessment can be useful, and further therapy can be considered if MRD is detected.[49] The role of MRD as an endpoint in AL amyloidosis should be explored in future studies.

Case 5: an elderly lady with lymphadenopathy and an IgM monoclonal protein.

A 77-year-old woman was referred to a hematologist due to bilateral enlarged cervical lymph nodes. Subsequent investigations showed mediastinal and retroperitoneal lymphadenopathy (<2 cm). An IgMλ monoclonal component was detected. Blood tests were all normal. A lymph node biopsy showed amyloid deposits. No clonal lymphocytes or plasma cells were detected in her bone marrow. The patient was followed closely without therapy. After 2 years, bilateral, symmetrical, ascending, sensitive, peripheral neuropathy appeared, and the patient was referred to our center. The concentration of the monoclonal protein was 25 g/L, lambda FLC level 40 mg/L (dFLC 24, ratio 0.40), hemoglobin 11.5 g/dL, alkaline phosphatase 360 U/L (upper reference limit 150 U/L) with normal bilirubin and aminotransferases. Testing for anti-myelin-associated glycoprotein (MAG) and anti-ganglioside antibodies was negative. Nerve conduction studies showed a purely axonal pattern. There were no signs of amyloid cardiac or renal involvement. We repeated a bone marrow biopsy that showed a 7% clonal, CD20-positive lymphoplasmacytic infiltrate. The clone harbored both the $MYD88^{L265P}$ and the CXCR4 mutations. The patient was treated with bendamustine, rituximab, and dexamethasone, which was well tolerated, and after 4 cycles a low-dFLC response was reached (dFLC 4 mg/L, ratio 0.63, monoclonal component 10 g/L). Two more cycles were performed without improvement of hematologic response, while alkaline phosphatase normalized. The patient is hematologically and clinically stable 1 year after treatment discontinuation.

Comments on patient 5

Immunoglobulin M related AL amyloidosis is a distinct clinical entity which accounts for 6-10% of all AL amyloidosis cases.[83,84] Localized amyloid deposits are more common, as well as lymph nodes, peripheral nervous system, and lung involvement, and amyloid FLC levels tend to be lower. The level of cardiac biomarkers is prognostic, but liver involvement and peripheral neuropathy also predict a poor outcome and were incorporated in a staging system specific for IgM-AL amyloidosis.[84] Peripheral neuropathy is frequently symptomatic but it is not detected by nerve conduction studies. Having both peripheral nervous system and liver involvement, this patient classified stage III despite normal cardiac biomarkers.

In most patients with IgM-AL amyloidosis the clone can be detected in the bone marrow at diagnosis. The underlying clone can be a pure PC (in ~25% of cases) or a lymphoplasmacytic neoplasm (in ~65% of cases) as in the present case, and this is relevant for the choice of treatment.[85] Lymphoplasmacytic clones harbor the MYD88 (95%-97%), CXCR4 (30%-40%), ARID1A (17%), and CD79B (8%-15%) mutations. Patients with IgM-AL amyloidosis caused by pure plasma cell clones should be treated like patients with non-IgM-AL amyloidosis; whereas patients with lymphoplasmacytic clones are generally treated with rituximab-containing regimens, based on treatments developed in Waldenström macroglobulinemia. Rituximab can be combined with dexamethasone and cyclophosphamide, bortezomib or bendamustine.[86-88] Patients with IgM-AL amyloidosis can also successfully undergo autologous stem cell transplant.[89] Ibrutinib can be an option in patients with favorable mutational pattern, but a first report highlighted a rather poor tolerability and scarce efficacy of this drug.[90] Patients with IgM-AL amyloidosis have lower response rates and shorter survival than other patients with AL amyloidosis when adjusted to stage.[85]

Neuropathy was the main reason to start treatment in this subject. The differential diagnosis of monoclonal gammopathies of neurological significance (MGNS) is challenging.[91] In this patient age was considered a contraindication to ASCT and we preferred a bortezomib-free combination due to neuropathy. The validated response criteria of the International Society of Amyloidosis consistently predict survival and can be used in IgM-AL amyloidosis.[84]

Conclusion

After many years of empirical treatment, the therapy of patients with AL amyloidosis has now entered the realm of evidence-based medicine, with three international clinical trials completed in the last two years.[44,73,92] We should now further exploit these achievements with new controlled trials based on validated endpoints. Yet, our evidence-based knowledge only covers a small part of the management of patients with AL amyloidosis. Daratumumab-bortezomib combinations can be used frontline in almost all patients, and the key eligibility criteria to safely proceed to ASCT are now shared by referral centers. However, important questions, such as best treatment at relapse, role of maintenance, the most cost-effective approach in patients with specific chromosomal abnormalities still need to be answered in controlled studies. For these reasons, patients should still be referred to specialized centers and treated within clinical trials whenever possible. With a growing therapeutic armamentarium survival has more than tripled; however, no progress was made in stage IIIb patients. Amyloid-directed therapy is an appealing opportunity to accelerate recovery of organ function, particularly in these patients. New therapies are emerging, and more than 20 interventional trials are now recruiting. Immunotherapies showing promise in MM will hopefully be offered to patients with AL amyloidosis. The anti-CD38 antibody isatuximab showed encouraging results in a recent phase II clinical trial in relapsed/refractory patients (NCT03499808).[93] Other PC antigens will likely be targeted by chimeric antigen receptor T-cells, bispecific T-cell engager antibodies, and antibody-drug conjugates such as belantamab mafodotin are being evaluated in a European trial (NCT04617925). Finally, the continuous, stimulating progress in basic and translational research are offering new insights in the mechanisms of disease and there is hope that new treatment targets will eventually be made available.

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Table 1. Criteria for hematologic and organ response

Hematologic response	Criteria
Complete response (CR)	Both criteria must be met: • Absence of amyloidogenic light chains (either free and/or as part of a complete immunoglobulin) defined by negative immunofixation electrophoresis of both serum and urine. • Either a FLC ratio within the reference range or the uninvolved FLC concentration is greater than involved FLC concentration with or without an abnormal FLC ratio
Very good partial response (VGPR)	dFLC <40 mg/L
Partial response (PR)	dFLC decrease of greater than 50%
No response (NR)	Less than a partial response
Organ response	**Criteria**
Cardiac response	Decrease of NT-proBNP by >30% and 300 ng/L (if baseline NT-proBNP >650 ng/L)
Renal response	At least 30% decrease in proteinuria or drop below 0.5 g/24 hour, in the absence of renal progression defined as a >25% decrease in eGFR
Hepatic response	50% decrease in abnormal alkaline phosphatase value or decrease in radiographic liver size by at least 2 cm

FLC, free light chain; dFLC, difference between involved and uninvolved free light chain.

Hematologic, cardiac, and renal response criteria have been validated,[39,51] while hepatic response criteria have been obtained by consensus.[52] A value adequate to measure hematologic response is deemed to be 50 mg/L. For patients with dFLC between 50 and 20 mg/L hematologic response other than complete response (ungraded) is reached when dFLC falls below 10 mg/L.[53,54]

Table 2. Pre-symptomatic hints, symptoms and signs leading to the diagnosis of AL amyloidosis.

Pre-symptomatic	Symptomatic		
➢ Increased markers of possible amyloid organ involvement: • Heart: NT-proBNP • Kidney: Albuminuria • Liver: Alkaline phosphatase monitored during follow-up of MGUS patients, and particularly in those with abnormal FLC ratio, and LC propensity to form amyloid (glycosylated k LCs, use of LC genes IGLV6-57, IGLV2-14, IGLV1-44, and LCs identified by machine learning algorithm)	Organ involved	Symptoms	Signs
	Heart	Reduced exercise tolerance Dyspnea at rest or exertion Fatigue Syncope Angina	Lower extremity edema Pleural effusions Jugular vein distension Arrhythmia Thickened ventricular walls and low voltages on ECG
	Kidney	Loss of appetite Fatigue and weakness	Lower extremity edema Anasarca
	Soft tissues	Jaw or buttock claudication Carpal tunnel (often bilateral) Dysarthria	Periorbital (upper body) purpura Macroglossia Nail dystrophy Shoulder pad Arthropathy Myopathy
	Peripheral nervous system including autonomic nervous system	Length dependent sensory-motor neuropathy Lipothymia Taste alterations Early satiety	Orthostatic hypotension Intestinal dysmotility Erectile dysfunction Voiding dysfunction
	Liver	Right upper quadrant tenderness Jaundice Early satiety	Hepatomegaly Weight loss
	Gastrointestinal tract	Abdominal discomfort	Malabsorption Gastrointestinal bleeding Diarrhea Weight loss

Table 3. Anti-amyloid therapies currently under development for AL amyloidosis

Agent	Target	Comments
CAEL-101	Amyloid fibrils	• Targets amyloid deposits in vivo as assessed by imaging studies • Promising results in preliminary uncontrolled studies[94] • Phase III trials comparing CyBorD versus CyBorD plus CAEL-101 in stage IIIa (NCT04512235) and IIIb (NCT04504825) subjects are ongoing
Birtamimab	Amyloid fibrils	• Post hoc analysis of the phase III study of birtamimab vs. placebo plus bortezomib-based upfront therapy suggests survival benefit in Mayo Clinic 2012 stage IV patients • A trial is now planned in Mayo Clinic 2012 stage IV patients
Doxycycline	Amyloid deposits Amyloid light chains	• Reduces LC proteotoxicity and inhibits the formation of and disrupts amyloid fibrils in animal models[95,96] • Two retrospective controlled studies reported a survival advantage with doxycycline[97,98] • A phase 2 trial of doxycycline in conjunction with bortezomib-based chemotherapy showed low early mortality rates[99] • An international randomized phase III trial of bortezomib-based therapy with or without doxycycline is ongoing (NCT03474458) • A Chinese randomized phase III trial of CyBorD with or without doxycycline has been completed and final results are awaited (NCT03401372)

CyBorD, cyclophosphamide, bortezomib, dexamethasone.

Table 4. Supportive therapy in AL amyloidosis[70]

Condition	Supportive measures
Fluid retention	• Salt restriction • Careful administration of diuretics (furosemide or torasemide, spironolactone) Liberal use can worsen hypotension and reduce pre-load which can exacerbate cardiac dysfunction
Hypotension	• Fitted elastic stockings • Midodrine, droxidopa, and pyridostigmine
Neuropathy	• Gabapentin and pregabalin • Serotonin-norepinephrine reuptake inhibitors (duloxetine and venlafaxine)
Diarrhea	• Loperamide • Octreotide in patients who are refractory to loperamide
Malnutrition	• Nutritional counselling and support
End stage renal disease	• Dialysis • Renal transplant in eligible patients with adequate hematologic response (CR/VGPR)[100]
Heart failure	• Beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers should be used with great caution in cardiac amyloidosis • Heart transplant in eligible young patients with severe heart damage and with minimal or no extracardiac involvement. This should be followed by effective chemotherapy. Risk-adapted chemotherapy while on transplant list is recommended under intensive monitoring

CR, complete response; VGPR, very good partial response.

Legends to figures

Figure 1. Diagnostic algorithm in symptomatic patients

DPD, Scintigraphy with ^{99m}technetium 3,3-diphosphono1,2-propanodicarboxylic acid; FLC, circulating free light chains; HMDP, scintigraphy with ^{99m}technetium-hydroxymethylene diphosphonate; PYP, scintigraphy with ^{99m}technetium-pyrophosphate; SIFE, serum immunofixation electrophoresis; UIFE, urine immunofixation electrophoresis.

*In patients with a monoclonal protein, amyloid deposits should be searched also in the bone marrow biopsy.

Ideally, AL amyloidosis should be diagnosed at a pre-symptomatic stage. When amyloidosis is suspected the first step should be searching for a monoclonal protein with sensitive technology. Patients with suspect cardiac involvement in whom monoclonal components are not detected may undergo a biopsy-free diagnostic process.[58] Scintigraphy with bone-seeking tracers, such as DPD, PYP, and HMDP can diagnose ATTR amyloidosis without a biopsy in the absence of a plasma cell dyscrasia, but cardiac uptake can be seen also in patients with AL amyloidosis. In the presence of a monoclonal component biopsy-based diagnosis and typing with mass spectrometry,[101] or, in highly specialized laboratories, with immunohistochemistry or immuno-electron microscopy[102] are mandatory. Amyloid deposits can be demonstrated with minimally invasive procedures, such as biopsy of abdominal fat, bone marrow and minor salivary glands. Abdominal fat aspirate has excellent feasibility and good sensitivity (~85% when associated with bone marrow biopsy) in AL amyloidosis.[102] If less invasive biopsies are negative, a biopsy of an affected organ will typically be required. Genetic testing allows discrimination between hereditary and wild-type TTR amyloidosis and identification of rarer hereditary variants.

Figure 2. Stratification of 1378 patients with AL amyloidosis according to the validated staging systems.

A. European modification of the Mayo Clinic 2004 staging system.[31,35]

The staging system is based on N-terminal pro-natriuretic peptide type B (NT-proBNP) and cardiac troponin (cTn). Troponin I was used in this figure. Cutoffs are 332 ng/L for NT-proBNP and 100 ng/L, 35 ng/L, and 54 ng/L for cTnI, cTnT, and high-sensitivity cTnT, respectively. B-type natriuretic peptide can substitute NT-proBNP in the staging system (cutoff 81 ng/L).[36] Stage I, II, and III patients have none, one, or two markers above the cutoff. Stage III patients are classified as stage IIIa or IIIb according to concentration of NT-proBNP below or above 8500 ng/L.

B. Revised Mayo Clinic staging system.[37]

The staging system is based on N-terminal pro-natriuretic peptide type B (NT-proBNP), cardiac troponin (cTn), and difference between involved and uninvolved free light chains (dFLC). Cutoffs are 1800 ng/L for NT-proBNP and 25 ng/L for cTnT. Troponin I can substitute cTnT (cutoff 70 ng/L)[38] and was used in this figure. Stage I, II, III, and IV patients have none, one, two, or three markers above the cutoff.

C. Renal staging system.[39]

The staging system is based on estimated glomerular filtration rate (eGFR) and proteinuria. Cutoffs are 50 mL/min per 1.73 m^2 for eGFR and 5 g/24h for proteinuria. Stage I, II, and III patients have none, one, or two markers above the cutoff.

Figure 3. Upfront treatment algorithm for AL amyloidosis

ASCT, autologous stem cell transplantation; BMDex, bortezomib, melphalan and dexamethasone; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; CR, complete response; Dara-CyBorD, daratumumab, cyclophosphamide, bortezomib, and dexamethasone; NT-proBNP, N-terminal pro-natriuretic peptide type-B; OR, organ response; VGPR, very good partial response.

At our center, the first step in the design of the therapeutic strategy is assessing eligibility for ASCT. However, the role of ASCT in AL amyloidosis is not supported by controlled trials and is challenged by the availability of very effective treatments like Dara-CyBorD. Yet, large long term outcome studies, that are lacking for newer combinations, show that ASCT grants long lasting responses with a prolonged improvement in survival.[40] At our center, eligibility for stem cell transplant with full dose (200 mg/m^2) melphalan requires:

age <70 years, Eastern Cooperative Oncology Group performance status <2, NT-proBNP <5000 ng/L, troponin T <60 ng/L, left ventricular ejection fraction >45%, New York Heart Association class <III, systolic blood pressure ≥100 mmHg, glomerular filtration rate >50 mL/min unless on dialysis, bilirubin <2 mg/dL, and diffusing capacity of the lungs for carbon monoxide >50%. At some referral centers, including ours, transplant is performed only in patients who are eligible to full dose melphalan.[42] Eligibility can be extended with a risk-adapted conditioning dose of melphalan (100-140 mg/m^2).[103] However, there is no evidence that reduced-dose melphalan is better than bortezomib–based chemotherapy and this approach is even more challenged by newer powerful non-transplant regimens.[44,104]Induction should be performed with Dara-CyBorD. If daratumumab is not yet available CyBorD can be used. In subjects who have contraindications to bortezomib (e.g., peripheral neuropathy), daratumumab-based induction without bortezomib may be considered, or ASCT can be performed upfront. In some cases, a satisfactory response (CR or VGPR, accompanied by cardiac response), can be achieved after induction alone. In these cases, treatment can be discontinued, and close monitoring initiated to detect hematologic relapse before this causes progression of organ involvement. This sequential approach reduces treatment-related mortality to less than 1% and allows fully exploiting modern powerful regimens also in transplant-eligible patients. [45-47] This approach is adopted at some referral centers, but it is not supported by controlled studies. If patients achieve less than a satisfactory response after ASCT, consolidation with bortezomib may improve the outcome.[105] Dara-CyBorD is a new standard of care for patients who do not undergo ASCT. In patients who are potentially eligible for transplantation, melphalan should be avoided. In elderly individuals BMDex may be considered. Patients with contraindications to bortezomib can be treated with MDex. Patients with advanced cardiac involvement (stage IIIb) should start bortezomib based treatment immediately, with attenuated dosages, and under close medical control. Cardiac transplant may be considered.

Figure 4. Rescue treatment algorithm for AL amyloidosis

ASCT, autologous stem cell transplantation; BMDex, bortezomib melphalan and dexamethasone; CR, complete response; Dara, daratumumab; Dex, Dexamethasone; Ixa, Ixazomib; Len, lenalidomide; MDex, melphalan and dexamethasone; OS; overall survival; PFS, progression free survival; Pom, pomalidomide; VGPR, very good partial response.

Relapsed/refractory patients should be enrolled in clinical trials whenever possible. Treating relapsed patients with a different class of agents than that used in upfront therapy is associated with prolonged PFS but has no impact on OS.[106] Thus, if response to the previous line of therapy lasted at least 12-18 months, re-treatment with the same drugs can be considered. Eligible patients who did not perform ASCT can be transplanted at relapse. At present, many relapsing patients have not been exposed to daratumumab, and this agent alone or combined with bortezomib or lenalidomide can be used safely and effectively at relapse.[65,67,107] Immune modulatory drugs are commonly used in the treatment of relapsed/refractory patients with AL amyloidosis. Lenalidomide and pomalidomide grant hematologic response in approximately 50% of patients with generally low (~15%) CR rates, and can rescue patients who are refractory to alkylators, proteasome inhibitors and other IMiDs.[108,109] IMiDs cause an increase in cardiac biomarkers that interferes with the assessment of cardiac response, and lenalidomide may worsen renal function in subjects with elevated proteinuria.[110] The second-generation, orally-available proteasome inhibitor ixazomib is active in patients previously exposed to bortezomib.[92,111] Recent studies reported high CR/VGPR rates (~80%) in relapsed/refractory patients with t(11;14) treated with venetoclax.[27] Bendamustine can be considered in patients with IgM-AL amyloidosis.

Figure 1.

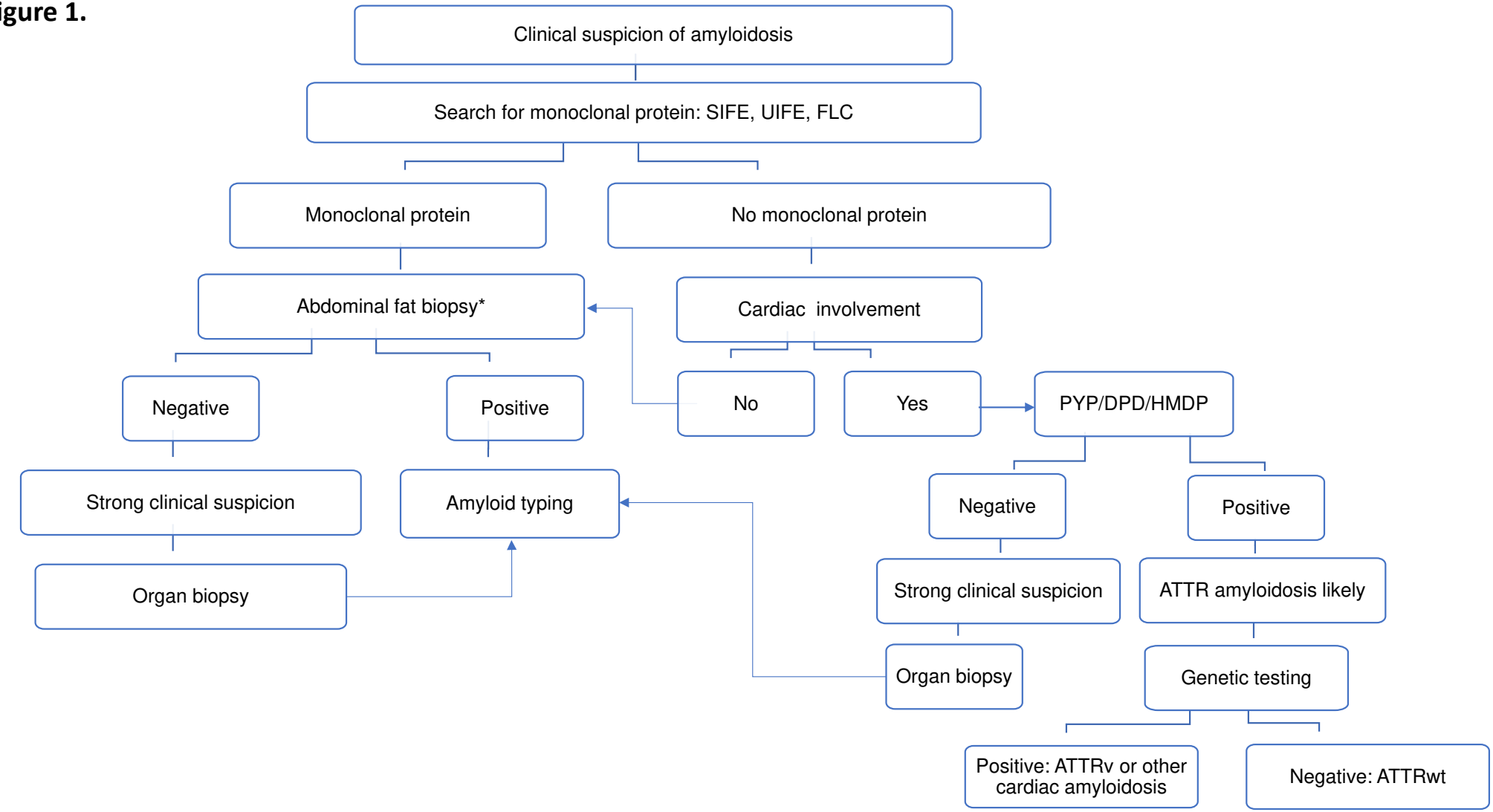
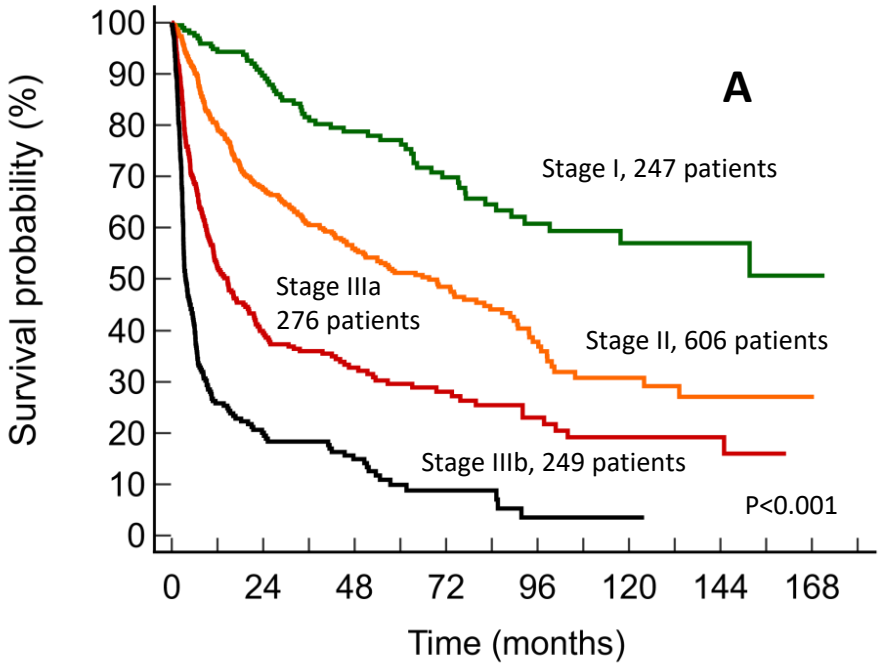
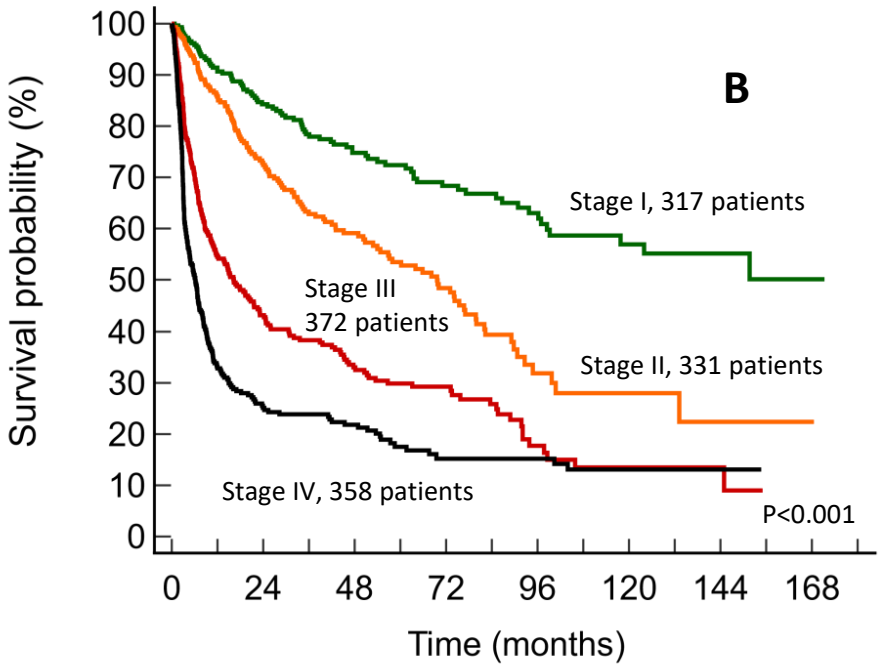

Clinical suspicion of amyloidosis
Search for monoclonal protein: SIFE, UIFE, FLC
Monoclonal protein
No monoclonal protein
Abdominal fat biopsy*
Cardiac involvement
Negative
Positive
No
Yes
PYP/DPD/HMDP
Strong clinical suspicion
Amyloid typing
Negative
Positive
Organ biopsy
Strong clinical suspicion
ATTR amyloidosis likely
Organ biopsy
Genetic testing
Positive: ATTRv or other cardiac amyloidosis
Negative: ATTRwt

Figure 2.


A
Survival probability (%)
Stage I, 247 patients
Stage IIIa
276 patients
Stage II, 606 patients
Stage IIIb, 249 patients
P<0.001
Time (months)


B
Survival probability (%)
Stage I, 317 patients
Stage III
372 patients
Stage II, 331 patients
Stage IV, 358 patients
P<0.001
Time (months)

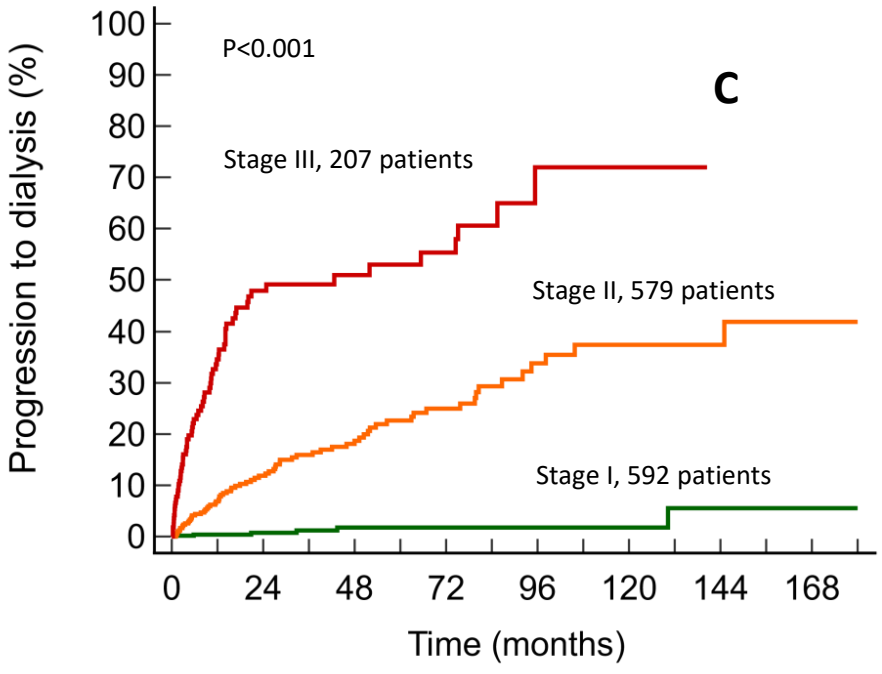
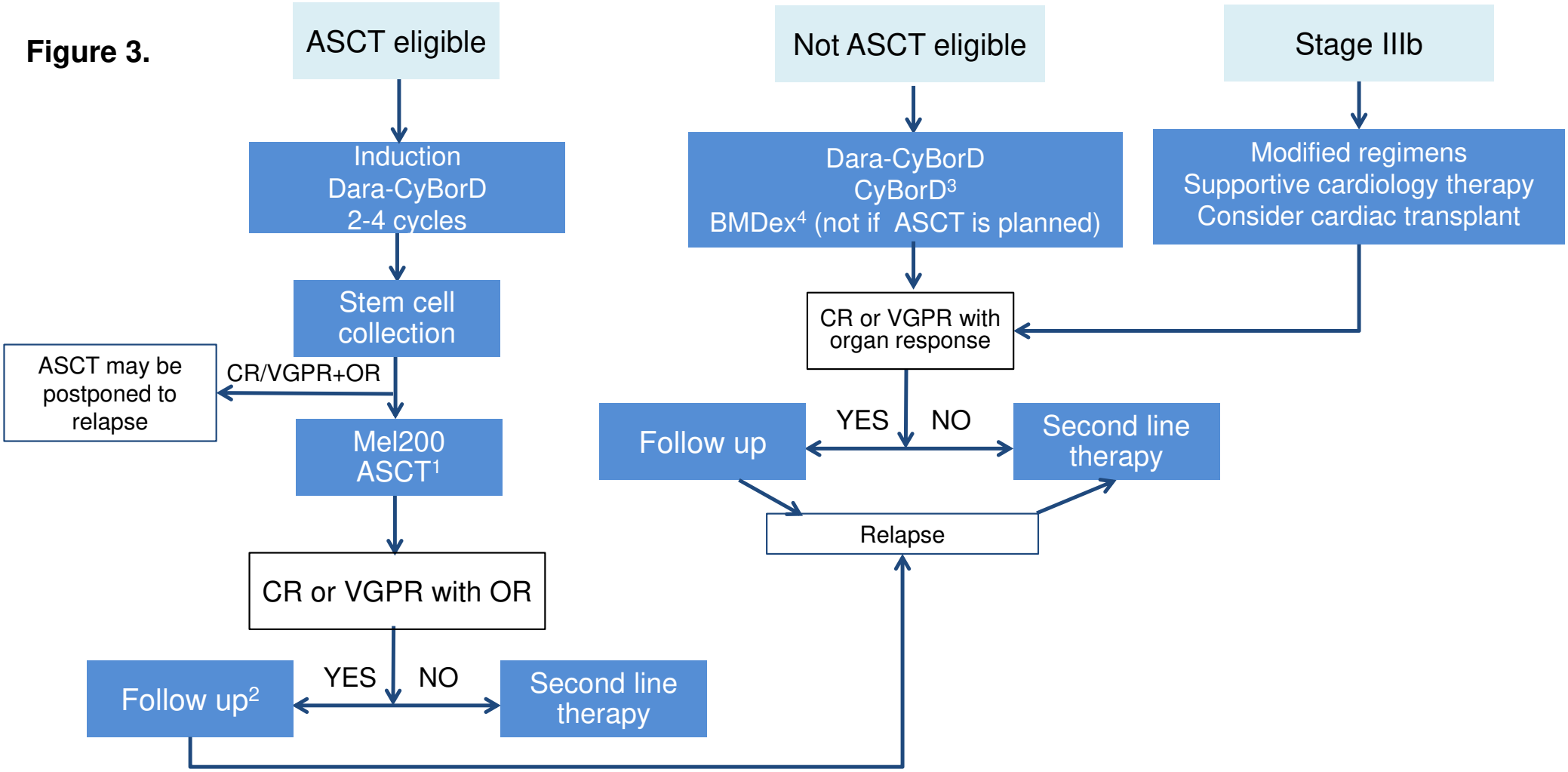
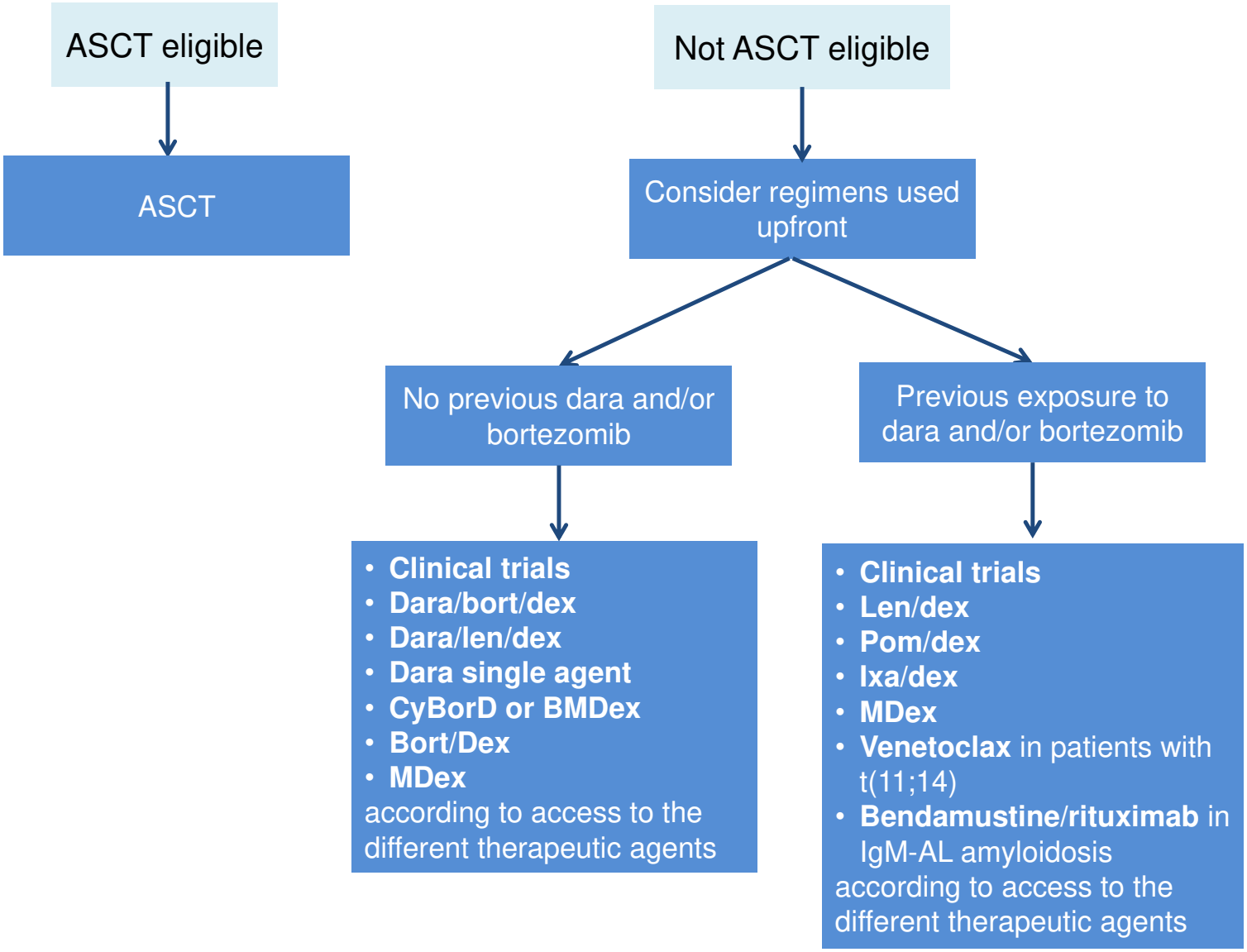

C
P<0.001
Progression to dialysis (%)
Stage III, 207 patients
Stage II, 579 patients
Stage I, 592 patients
Time (months)

Figure 3.



1. For patients with eGFR <30mL/min, Mel140 may be considered
2. For patients with multiple myeloma, consider maintenance
3. If daratumumab is not available
4. For patients with severe neuropathy, MDex can be considered

Figure 4.


ASCT eligible
ASCT
Not ASCT eligible
Consider regimens used upfront
No previous dara and/or bortezomib
Previous exposure to dara and/or bortezomib
• Clinical trials
• Dara/bort/dex
• Dara/len/dex
• Dara single agent
• CyBorD or BMDex
• Bort/Dex
• MDex
according to access to the different therapeutic agents
• Clinical trials
• Len/dex
• Pom/dex
• Ixa/dex
• MDex
• Venetoclax in patients with t(11;14)
• Bendamustine/rituximab in IgM-AL amyloidosis
according to access to the different therapeutic agents