

REVIEW

Multiple myeloma-associated AL amyloidosis: is a distinctive therapeutic approach warranted?

NJ Bahlis¹ and HM Lazarus²

¹Department of Medicine, Tom Baker Cancer Center, University of Calgary, Calgary, Alberta, Canada and ²Comprehensive Cancer Center of Case Western Reserve University and University Hospitals of Cleveland, Cleveland, OH, USA

The natural history of multiple myeloma (MM) was revolutionized by the introduction of haematopoietic stem cell transplantation to the treatment armamentarium of this disease. Defined subgroups of MM patients (such as the elderly or dialysis-dependent) have required an individualized approach in order to minimize the transplant-related mortality. Little, however, is known about the management of 12–30% of MM patients with coexistent AL amyloidosis as the amyloidopathy is often overlooked and when recognized these patients commonly are excluded from clinical trials. While occult amyloidosis appears to have no impact on the toxicity and outcome of MM patients, the presence of symptomatic amyloidopathy clearly worsens their prognosis. Use of induction chemotherapy drugs that can cause further damage to the heart (Adriamycin), nervous system (Vincristine) or kidneys should be avoided as should lengthy delays in proceeding to autograft. Further, refining the transplant eligibility criteria for this subgroup of patients with co-existent amyloidopathy to include the number of organs involved and the degree of cardiac involvement (NYHA class, Troponins and NT-pro-BNP levels) along with melphalan dose-adjustment will minimize the treatment-related toxicity and mortality and possibly allow a reversal of the organ damage induced by the amyloidogenic light chain.

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Introduction

Multiple myeloma is a clonal malignancy of terminally differentiated B lymphocytes characterized by the expansion of clonal plasma cells in the bone marrow resulting in suppression of normal haematopoiesis, production of monoclonal immunoglobulins or fragments (light or heavy

chain), immunosuppression, nephropathy and neuropathy. These findings often result from direct injury or accumulation of immunoglobulins (heavy or light chain) in various organs. The toxic effects and organ dysfunction caused by immunoglobulin deposition, however, differ in severity, clinical presentation and prognosis from that caused by 'amyloidogenic' light chain deposition as seen in AL amyloidosis. While 12–15% of patients develop overt clinical amyloidosis through the course of their disease, up to 30% of myeloma patients are found to have subclinical amyloid deposits in subcutaneous fat pad aspirates, bone marrow biopsies and biopsies of other vital organs such as heart, liver and kidneys.^{1–3} Little is known about the prognosis and optimal management of these patients with sub-clinical amyloidopathy as they are often unrecognized, or are excluded from clinical trials when overt clinical amyloidosis is present.

Symptoms and signs of amyloid organ involvement such as dyspnea that is disproportionate to the degree of anemia, proteinuria with predominant albuminuria, neuropathy with autonomic dysfunction, often are mistakenly considered to be related to multiple myeloma. Under-recognition of subclinical amyloidosis amongst myeloma patients has invariably resulted in a suboptimal care and poor transplant outcomes of this subgroup of patients. For instance, while melphalan at a dose of 200 mg/m² (or greater) is the preferred conditioning regimen in multiple myeloma,^{4,5} AL amyloid patients with cardiac or more than two organ involvement represent an intermediate risk group; such patients may require dose reduction of the melphalan conditioning in order to avoid life-threatening complications after stem cell transplantation.⁶ Similarly myeloma patients with amyloid cardiac involvement should be monitored for life-threatening bradycardia if they are treated with thalidomide.^{7,8} Therefore, it is crucial to recognize the presence of AL amyloidosis in the setting of multiple myeloma, in particular, when making therapeutic decisions regarding the choice of induction therapy or the intensity of the conditioning regimen.

Biology and genetics of AL amyloidosis

Amyloid is an extracellular deposit of autologous proteins that produces a characteristic apple-green birefringence

Correspondence: Dr NJ Bahlis, Department of Medicine, Tom Baker Cancer Center, University of Calgary, 1403 29th St NW, Rm 681, Calgary, Alberta, Canada T2N 4N1.
E-mail: nbahlis@ucalgary.ca
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when viewed under polarized light after Congo red staining. Electron microscopy reveals the amyloid protein to appear as rigid unbranched aggregates of fibrils of indefinite length. These fibrils are composed predominantly of proteins arranged in anti-parallel, cross β -pleated sheet configuration with strands perpendicular to the long axis of the filament. This material is insoluble, resistant to proteolytic degradation and has an intriguing tropism for specific organs including kidney, heart, liver, spleen, lung, gastrointestinal tract, skin and peripheral nerve.⁹ The mechanism of organ damage caused by the amyloid protein is yet unknown; however, organ dysfunction appears reversible as the amyloid deposits frequently regress when the supply of the fibril precursor is eradicated. The most common form of amyloidosis in Western countries is AL amyloidosis, which results from accumulation and organ deposition of light chain immunoglobulin (most commonly λ) or rarely a fragment of a heavy chain. In most instances the disease is systemic although localized amyloidosis involving the urinary tract, tracheobronchial tree, conjunctiva and thyroid are well described.¹⁰

The degree of plasma cells infiltration of the bone marrow in AL amyloidosis usually is minimal, commonly less than 10% (although some patients have more than 20%)² and such cells typically have a very low proliferative index as depicted by their low bromodeoxyuridine uptake.¹¹ The cell responsible for production of the structurally abnormal monoclonal light chain in AL amyloidosis recently was elucidated. Using anti-idiotypic monoclonal antibodies as probes, Perfetti *et al.*¹² identified in the bone marrow three types of amyloidogenic post-germinal center monoclonal B lymphocytes (very late stage B lymphoid cells, lymphoplasmacytoid and plasma cells) and a subset of circulating peripheral blood B lymphocytes that have undergone heavy chain class-switching and expressed the same idiotype as the patient's amyloid chain. Using RT-PCR with primers specific for the CDR sequence of the patient's amyloid light chain, the presence of this circulating B-cell clone was confirmed.¹³

Genetic studies in AL amyloidosis have revealed high genetic instability similar to that reported with MGUS and myeloma. Classic cytogenetic studies in this disease previously were limited by the scarcity of plasma cells in the bone marrow and their low proliferative index. The use of interphase fluorescent *in situ* hybridization (FISH) along with plasma cell enrichment techniques has allowed investigators to detect common IgH translocations similar to that previously reported in MGUS and myeloma patients.^{14,15} Translocations involving the IgH (14q23) were seen in 72.4% of the AL amyloid patients in one series with 11q13 as translocation partner in 76.2% of the cases.¹⁴ The overall prevalence of t(11;14) in AL amyloidosis is 55% compared to 15% in multiple myeloma.¹⁵ 4p16 also was reported as a translocation partner for the IgH with t(4;14)(p16.3;q32) found in 14% of AL amyloid patients, a frequency similar to that reported in non-amyloid myeloma cases (15%).¹⁶ These findings support the concept, already adopted for MGUS and myeloma, of IgH primary translocation as an early pathogenic event in AL amyloidosis as well.^{17,18} Despite their commonality to these early pathogenic events, however, AL amyloidosis is a molecularly distinct entity from multiple myeloma. Gene expression analysis identified a subset of 12 genes that are differentially expressed in myeloma and AL amyloidosis patients.¹⁹ This subset of genes included among others, genes that regulate plasma cell death and apoptosis like *TNFRSF7*, a member of the tumor necrosis factor superfamily with higher expression in AL plasma cells. Another gene of interest is the chemokine SDF1 (CXCL12), endogenous ligand for CXCR4, which is expressed at a significantly higher rate in AL plasma cells in comparison with myeloma plasma cells. Table 1 lists some of the genes that are relevant to the pathogenesis of AL amyloidosis and are differentially expressed between AL amyloidosis and multiple myeloma. Despite some similarity with other plasma cell disorders, AL amyloidosis is a well-defined clinical entity, with a distinct phenotype; understanding the molecular and genetic events that result in this character-

Table 1 Relevant genes with significantly higher (\uparrow) or lower (\downarrow) expression in AL plasma cells (ALPC) compared to myeloma plasma cells (MMPC)

Gene symbol	Name of gene	Expression in ALPC vs MMPC	Gene function
<i>RB1/Rb</i>	Retinoblastoma	\uparrow	Role in cell cycle regulation and apoptosis
<i>CCND1</i>	Cyclin D1	\uparrow	Required for cell cycle G1/S transition
<i>NFKB1A</i>	Inhibitor of nuclear factor of κ light chain gene enhancer in B cells	\uparrow	Regulates NF κ B, ICAM1, RELA, RELB
<i>CXCL12</i>	SDF1	\uparrow	Chemokine, cell migration and invasion
<i>MYC</i>	v-myc myelocytomatosis viral oncogene homolog	\downarrow	Role in cell cycle progression, apoptosis and cellular transformation
<i>p53</i>	Tumor protein p53	\downarrow	Regulation of cell cycle, specifically in the transition from G0 to G1
<i>E2A</i>	E2A immunoglobulin enhancer binding factors E12/E47	\downarrow	Regulates B-cell development
<i>XRCC5</i>	Ku80	\downarrow	Repair of DNA double-strand break
<i>IL6ST</i>	IL6 signal transducer	\downarrow	Signal transducer shared by many cytokines, including interleukin 6 (IL6)
<i>CASP3</i>	Caspase 3	\downarrow	Role in the execution-phase of cell apoptosis
<i>CDK4</i>	Cyclin-dependent kinase 4	\downarrow	Important for cell cycle G1 phase progression; responsible for the phosphorylation of retinoblastoma gene product (Rb).

(Modified from Abraham *et al.*¹⁹).

istic phenotype is of essence as it will lead to the identification of novel therapeutic targets that may alter the natural history of the disease.

Diagnosis of multiple myeloma associated AL amyloidosis

AL amyloidosis and multiple myeloma share several clinical features such as clonal plasma cells and the production of monoclonal immunoglobulins; however, the hallmark of the amyloid monoclonal light chain is its propensity to form insoluble fibrils with specific tropism for variable organs. Hence, the diagnosis of AL amyloidosis requires histological confirmation with a biopsy specimen staining positive with Congo red and demonstrating apple green birefringence under polarized light.

A concurrent diagnosis of AL amyloidosis is made at presentation or sometime during the course of the myeloma in 10–15% of patients.^{1,2} This diagnosis requires fulfilling diagnostic criteria for both conditions including histological confirmation of amyloid fibrils deposition and other myeloma-specific criteria such as hypercalcemia, lytic bone lesions and anemia. It should be cautioned, however, that the mere presence of bone marrow plasmacytosis is an insufficient criterion to establish the diagnosis of multiple myeloma as 18% of AL amyloidosis patients are reported to have more than 20% light chain restricted plasma cells in the bone marrow without any other myeloma-specific features.² Similarly, the presence of nephropathy could result from either conditions and should not be used to make the diagnosis of amyloidosis unless histologic confirmation is obtained to support the diagnosis. In multiple myeloma, nephrotic syndrome is relatively rare (typically proteinuria is <3g/24 h in about 34% of the patients) and mainly Bence-Jones protein is found in the urine with low amounts of albumin. Typical histological features of myeloma-induced nephropathy

include tubular injury with hyaline fractured casts in distal tubuli and the collecting ducts while in AL amyloidosis kidney biopsies reveal hyaline deposits in the mesangium and along the glomerula basement membrane and capillary loops with the characteristic Congo red staining. Amyloid deposit may also be found in small arteries and the tubular basement membrane.²⁰ Clinically amyloid nephropathy predominantly presents as nephrotic syndrome and less commonly as an acute tubular injury like picture when tubular amyloid deposition leads to tubular ischemia.

Although physical findings of amyloidosis are specific (enlargement of the tongue, periorbital purpura, shoulder pad sign), relying on symptoms and signs alone without entertaining the possibility of the co-existence of amyloid in myeloma patients inevitably may result in overlooking this additional condition and potentially significant therapeutic consequences. Therefore, amyloidosis should always be suspected in any myeloma patient with nephrotic range proteinuria, infiltrative cardiomyopathy, autonomic neuropathy, hepatomegaly and symptoms of partial bowel-obstruction. Table 2 summarizes symptoms and signs of amyloid organ involvement in patients with myeloma. It should be noted that subclinical amyloidosis was reported at a much higher frequency (35%) among myeloma patients when routine fat pad biopsies and Congo red staining of the bone marrow biopsies were performed in a study conducted at the University of Arkansas.³ According to that report the clinical and therapeutic value of such findings appears to be insignificant and without any prognostic consequences in patients with asymptomatic or ‘occult’ amyloid deposition. Finally, it is important to perform immunohistochemical typing of the amyloid protein, even in the setting of a clonal plasma cell dyscrasia as other types of amyloidosis such as senile cardiac amyloidosis (ATTR amyloidosis with mutated transthyretin as the amyloidogenic protein) could be present along

Table 2 Clinical and laboratory features of amyloid organ involvement in patients with multiple myeloma

<i>Organ</i>	<i>Clinical and laboratory features suggestive of AL amyloidosis</i>
Kidney	Nephrotic range proteinuria, predominantly albuminuria
Heart	Non-hypertensive congestive heart failure with clean coronaries Electrocardiogram with low voltage, bradycardia, A-V block Cardiac Holter: arrhythmia with conduction delays (A-V block, branch or fascicular block) Echo: wall thickening (interventricular septum > 12 mm) and/or diastolic dysfunction High-serum troponins and brain natriuretic peptide (BNP or pro-BNP)
Liver	Hepatomegaly in the absence of heart failure (> 15 cm) Elevated serum alkaline phosphatase (> 1.5 × normal)
Nerve	Mostly sensory loss with paresthesias Carpal tunnel syndrome Autonomic neuropathy (diarrhea, constipation, vomiting, orthostatic hypotension, impotence)
GI tract	Macroglossia Early satiety, diarrhea, chronic nausea, malabsorption. Bowel perforation and rectal bleeding
Lung	Dyspnea disproportionate to the degree of anemia, diffuse interstitial lung infiltrates
Soft tissue	Periorbital purpura, lymphadenopathy, claudication of limbs or jaw, muscle hypertrophy, seronegative arthropathy

with the clonal immunoglobulin in the serum or urine of myeloma patients.

Role of autologous stem cell transplantation in the treatment of AL amyloidosis and multiple myeloma

Autologous transplant and multiple myeloma

Over the last two decades the treatment of multiple myeloma was improved by the introduction of high-dose therapy and stem cell rescue. The first evidence of a potential beneficial role for high-dose chemotherapy in the treatment of multiple myeloma dates back to the mid 1980s.²¹ Since then, five randomized trials have compared the outcome of patients treated with high-dose therapy (HDT) and standard dose therapy (SDT) (Table 3).^{22–26} Two studies, the Intergroup Français du Myelome (IFM90) and the Medical Research Council (MRC) VII, have shown a statistically significant improvement in complete remission rate, event-free survival (EFS) and overall survival (OS) in favor of HDT.^{22,23} With some caveats in their study design or execution, the remaining three randomized trials failed to reproduce these positive results. The US Intergroup trial showed no improvement in CR or OS for HDT compared to SDT, although it should be noted that 52% of the patients in the SDT arm were allowed to ‘cross-over’ to the transplant arm by design; an early vs late transplant comparison that confounded the results and their interpretation.²⁴ The Group Myelome-Autogreffe (MAG) reported a trend toward better EFS with HDT compared to SDT that did not translate into superior OS.²⁵ Similarly, the Spanish cooperative group PETHEMA found no difference in OS between the HDT and SDT arms despite higher CR rates with HDT (30 vs 11%). It should be noted, however, that only patients responding to induction treatments were enrolled into the PETHEMA study, a confounding factor that might explain

the lack of survival benefit with HDT (Table 3).²⁶ Finally, several groups have taken the approach of tandem transplantation to treat minimal residual disease. Results of the IFM94 study and a recent update from the Bologna group have demonstrated superior EFS and OS in favor of tandem transplant, in particular for the subsets of patients who failed to achieve CR or a very good partial response (>90% improvement in M protein) after a single transplant.^{27,28}

Autologous transplant and AL amyloidosis

The median survival from diagnosis of AL amyloid patients is 13 months and is far worse (<6 months) if symptoms of congestive heart failure are present at diagnosis.² Cyclic treatment with low-dose melphalan and prednisone are shown to improve the median survival of these patients (up to 17 months) yet therapy rarely induces hematologic CR or reversal of the organ damage.²⁹

Based upon the success of autologous stem cell transplant in multiple myeloma, investigators began applying the same approach to AL amyloidosis patients with the goal of eradicating the amyloidogenic plasma cell clone. The treatment of amyloidosis was demonstrated to be far more challenging than multiple myeloma because of the underlying organ damage, in particular, renal and cardiac dysfunction. The initial enthusiasm for this approach, as introduced by Comenzo *et al.*³⁰ in 1996, was rapidly tempered by the high transplant-related mortality (TRM) reaching 45%, in particular, when cardiac or multiorgan involvement was present. This high mortality rate with initial stem cell transplantation led investigators at the Mayo clinic and Boston University to propose a new risk-adapted patient selection criteria with adjustment of the melphalan conditioning dose. According to these criteria the presence of asymptomatic or compensated cardiac involvement renders the patient ‘intermediate risk’ and requires reduction of the melphalan dose from 200 to

Table 3 Randomized trials of autologous stem cell transplantation for multiple myeloma

Study	n	SDT ^a vs HDT ^b (P-value)			Study criticism and remarks
		CR (%)	Median EFS (months)	Median OS (months)	
IFM90 ²²	200	5 vs 22% (P<0.001)	18 vs 28 (P=0.01)	44 vs 57 (P=0.03)	No IFE was required for CR Bone marrow source of stem cells 26% did not proceed to HDT 9% in SDT arm → salvage HDT
MRC VII ²³	401	8 vs 44% (P<0.001)	19 vs 31 (P=0.001)	42 vs 54 (P<0.001)	Median 6 cycles only in the SDT arm 25% did not proceed to HDT 15% in the SDT arm → salvage HDT
MAG ²⁵	190	20 vs 36% P=NR	18 vs 25 (P=0.07)	53 vs 58 (P=0.91)	24% did not proceed to HDT 22% in SDT arm → salvage HDT
PETHEMA ²⁶	164	11 vs 30% (P=0.002)	33 vs 42 (P=NS)	61 vs 66 (P=NS)	Only responding patients were allowed to proceed to transplant
US Intergroup ²⁴	510	15 vs 17% (P=NS)	21 vs 25 (P=0.05)	53 vs 58 (P=NS)	High cross over rate (52%) by design

^aSDT = standard dose therapy.

^bHDT = high-dose therapy.

NR = not reported; NS = not significant.

Table 4 Criteria for AL amyloidosis patient selection for autograft and dose adjustment of melphalan conditioning.⁴

Good risk	Intermediate risk	Poor risk/ineligible
Any age and all criteria met: • 1 or 2 organs involved • No cardiac involvement • Creat clearance \geq 51 ml/min	Age < 71, any criteria: • 1 or 2 organs involved including cardiac or renal with creat clearance < 51ml/min • Asymptomatic or compensated cardiac involvement	Any criteria: • 3 organs involved. • Advanced cardiac involvement
<i>Melphalan dosing</i> • 200 mg/m ² if \leq 60 years • 140 mg/m ² if 61–70 years • 100 mg/m ² if \geq 71 years	<i>Melphalan dosing</i> • 140 mg/m ² if \leq 60 years • 100 mg/m ² if 61–70 years	Standard therapy Clinical trials

Table 5 Studies (with $n \geq 15$ patients) of high dose melphalan and autograft in AL amyloidosis

Study ^{ref.}	n	Melphalan dose (mg/m ²)	TRM (%)	Hematologic CR+PR (%)	Organ response (%)	Median OS (months)
Gertz <i>et al.</i> ³¹	120	200 or 140 + TBI	9.2	75	NA	NR
	51	100–140	20	53	NA	31.5
Mollee <i>et al.</i> ³²	20	140–200	35	56	Renal: 46 Liver: 50 Cardiac: 25	3-year OS: 56%
Perz <i>et al.</i> ³³	24	100–200	13	54	Renal: 50	3-year OS: 71%
Skinner <i>et al.</i> ³⁴	277	100–200	13	40 CR	44	55.2
Moreau <i>et al.</i> ³⁵	21	140–200	43	25 CR	83	4-year OS: 57%
Gertz <i>et al.</i> ³⁶	28	200	10	64	75	3-year OS: 62%
Chow <i>et al.</i> ³⁷	15	170–200	0	67 CR	79	4-year OS: 75%
Schonland <i>et al.</i> ³⁸	41	100–200	7	50 CR	40	2-year OS: 90.4%
Gillmore <i>et al.</i> ³⁹	40	100–200	38	40 CR	56	1-year OS: 60%
Perz <i>et al.</i> ⁴⁰	19	45–200	26	42	42	48
Vesole <i>et al.</i> ⁴¹	114	NA	25	32.5	36	3-year OS: 57%
Dispenzieri <i>et al.</i> ⁴²	63	100–200	NA	NA	NA	4-year OS: 71%
	63	Mel/Dex/Colchicine				4-year OS: 41%
Jaccard <i>et al.</i> ⁴³	37	140–200	24	64	52	48.6
	50	Mel 10 mg/m ² + Dex	—	65	40	56.9

^aCase control study.

^bOnly prospective randomized trial (NA = not available; NR = not reached).

140 mg/m² (or to 100 mg/m² in the more elderly). The presence of three or more organs involved or advanced cardiac disease deems the patient essentially ineligible for high-dose therapy (Table 4).⁶ With the introduction of these criteria the TRM was reduced by more than half and is currently in the range of 10–15%; therefore, patient selection and careful screening of organ involvement plays a crucial role on the decision to proceed with high-dose therapy as well as its outcome.

The currently available published literature in support of autologous transplantation in AL amyloidosis results mostly from retrospective non-randomized or matched case-control studies. A list of the largest studies and their results is summarized in Table 5.^{31–43} The largest study included 701 consecutively referred primary AL amyloidosis patients and reported that only 394 patients (56%) met eligibility criteria for transplantation.³⁴ The median survival was 4.6 years, and 100 day TRM rate was 13%. Patients who achieved a complete hematological response (40%) had a higher organ response rates and OS. A second pivotal retrospective study compared 63 autotransplant patients with 63 matched controls who received other treatments.⁴²

This study suggested a survival benefit of high-dose melphalan (HDM)/autograft at one (89 vs 71%), two (81 vs 55%) and four years (71 vs 41%) despite a reported TRM rate of 13%. These studies clearly suggest that autologous stem cell transplantation with high-dose melphalan (100–200 mg/m²) conditioning is an effective treatment for primary AL. To date, only one prospective randomized trial comparing autologous stem cell transplant vs oral melphalan and dexamethasone (M-Dex) has been completed.⁴³ In the autograft arm, with 74% of the patients receiving their planned treatment, the TRM was 24% compared to only 2% with M-Dex. Hematologic responses did not differ between the two arms. The Kaplan–Meier estimated median survival also was similar for both arms of the study (56.9 months for M-Dex arm vs 48.6 months for autograft; $P=0.2$). While a trend for better survival with autograft was seen in the referral centers ($P=0.38$), a significantly better survival in the M-Dex arm was noted in centers without extensive transplant experience ($P<0.006$). The results of this study should be analyzed with great caution as only 74% of the patients randomized to the transplant arm actually proceeded to

high-dose therapy and it is not clear whether patients with cardiac involvement ($n=23$) received full or intermediate dose melphalan for conditioning.

New staging system for AL amyloidosis

The results of the currently available studies in AL amyloidosis emphasize that the suggested superiority of autograft compared to oral melphalan-based regimen remains to be proven in a randomized, prospective trial. These data also underscore the need for new, powerful predictors of prognosis and TRM. The Mayo clinic group recently published a new staging system for AL amyloidosis using threshold values of N-terminal pro-brain natriuretic peptide (NT-proBNP) and either cardiac troponins T or I (NT-pro-BNP <332 ng/l; c-TnT <0.035 μ g/l; c-TnI <0.1 μ g/l).⁴⁴ Depending on whether NT-proBNP and troponin levels were both low, high for only one level or were both high, patients were classified as stage I, II or III, respectively. Using cTnT and NT-proBNP the survival of patients in stages I, II and III were 26.4, 10.5 and 3.5 months, respectively.⁴⁵ Therefore, this new staging system can be used as a powerful predictor of survival outcomes of AL amyloid patients receiving intensive therapy and autograft as well as a useful tool for stratifying patients in randomized clinical trials and comparing outcomes across studies. Finally, elevated levels of cardiac Troponin I (cTnI >0.1) was found (univariate regression analysis) to be predictive of high TRM.⁴⁴ Identifying *a priori* AL amyloid patients belonging to a poor risk group or those with high TRM will allow clinicians to consider such patients for enrollment into therapeutic clinical trials that employ novel agents rather than more toxic and potentially ineffective treatments.

High-dose therapy and autograft for multiple myeloma associated AL amyloidosis

When should AL amyloidosis be suspected in multiple myeloma patients?

In all, 12 to 15% of myeloma patients have symptomatic AL amyloidosis and up to 38% of newly diagnosed myeloma patients are found to have clinically occult AL amyloidosis.¹⁻³ In a series reported by Desikan *et al.*,³ Congo red stain of fat pad aspirates and bone marrow biopsies were found to be positive in 31 and 10% of newly diagnosed myeloma patients, respectively. Patients with occult AL amyloid deposits did not differ in their disease characteristics; in particular no λ light chain predominance was observed. No statistical difference in event free survival (59+ vs 52 months; $P=0.9$) or OS (59+ vs 66+ months; $P=0.9$) was observed between patients with and without 'occult' amyloidosis after single or tandem autologous stem cell transplantation.³

While clinically 'occult' AL amyloidosis does not appear to alter the survival outcomes of myeloma patients, the impact of such an association is not well documented among the subgroup of patients with symptomatic organ involvement. These patients are universally excluded from clinical trials conducted for either disease, which explains

the paucity of the literature describing the outcomes of patients with such an association. In the series by Desikan *et al.*³ the median OS of seven patients with 'symptomatic' amyloid organ involvement was 38 months compared to 59–66 months for the remainder of the patients either with clinically occult disease or no amyloid deposits.³ The Mayo clinic group recently reported that the presence of circulating peripheral blood plasma cells predicted poor outcome in AL amyloidosis. More importantly in their series AL patients with concurrent multiple myeloma had a poor prognosis with a median survival of only 14 months compared to 32 months for other AL patients.⁴⁶ No doubt patients with multiple myeloma and symptomatic AL amyloidosis are more 'fragile' than patients with myeloma alone as a result of severe dysfunction of several key organs, mainly heart and kidneys. Furthermore while the TRM of myeloma patients undergoing autograft is minimal ($<1-2\%$), it can reach 25–30% in AL amyloid patients, especially at centers with little or no experience in such subjects. A multidisciplinary approach often is required in the pre- and peri-transplant period of AL amyloid patients. Holter cardiac monitoring before transplant often is necessary to screen for cardiac arrhythmias. Aggressive management of the fluid balance in an intensive care unit setting using wedged pulmonary artery catheters after high-dose melphalan therapy sometimes is required as amyloid patients tend to 'experience fluid overloaded states' while they actually have depleted intravascular volumes secondary to hypoalbuminuria. Pre-transplant gastric and colonic endoscopies may be performed in patients with bowel motility symptoms to screen for gastrointestinal involvement to avoid bowel perforation. Therefore, it is crucial to recognize clinical features of amyloidosis in myeloma patients before proceeding to high-dose therapy (Table 2). Features such as severe nephrotic syndrome, nonischemic cardiomyopathy in non-hypertensive patient, hepatomegaly with elevated alkaline phosphatase, carpal tunnel syndrome, and symptoms of autonomic neuropathy (orthostatic hypotension, persistent vomiting, diarrhea or constipation, partial bowel obstruction, impotence) should be sufficient to initiate screening for amyloidosis induced organ damage. Unawareness of the significance of such features inevitably will result in deleterious consequences of high-dose therapy.

Is induction chemotherapy required in myeloma-associated AL amyloidosis?

Treatment of multiple myeloma with high-dose therapy and stem cell rescue is preceded by 'induction' therapy either with dexamethasone alone, combination chemotherapies (VAD, VBMCP, etc.) or more recently novel agents (thalidomide, lenalidomide and bortezomib) as monotherapy or in combinations with dexamethasone. The goal of such treatment is to enhance stem cell mobilization, minimize the degree of plasma cell contamination of the apheresis product and to reduce tumor burden *in vivo* before stem cell transplantation. The therapeutic utility of such approach and whether it has any impact on the survival outcomes post-transplant has never been tested in a prospective randomized trial.⁴⁷

Indeed, several non-randomized studies or retrospective reviews fail to show any correlation between response to induction chemotherapy before autograft and OS after transplant.^{48,49} Furthermore, attempts to achieve a better purging of the apheresis product either through *in vitro* purging with positive CD34 cells selection or through dose-intensification before transplant also failed to demonstrate any impact on post-transplant survival of myeloma patients.^{50,51}

The role of induction chemotherapy comes under further scrutiny in myeloma patients with associated amyloidosis. The group at Boston University prospectively compared two cycles of oral melphalan and prednisone followed by autotransplant vs autograft alone in AL amyloidosis patients (myeloma excluded).⁵² Their results indicated no additional benefit from induction chemotherapy with respect to survival, hematological or organ response. To the contrary, and despite a delay in autograft of only 9 weeks with induction treatment, patients with cardiac amyloidosis appeared to suffer a survival disadvantage. In all, 13% of the patients treated with initial oral chemotherapy could not proceed to autograft because of disease progression ultimately leading to death. In a similar study, induction chemotherapy with VAD before autograft did not result in any increase in either hematological response or survival parameters.³³ Based on these reports, it is recommended that transplant-eligible amyloidosis patients should proceed directly to stem collection with G-CSF alone without any prior induction chemotherapy. Such an approach will allow these patients to avoid any potential harmful effects of induction regimen and prevent any delay in proceeding into high-dose therapy.

Whether a similar approach should be adopted in myeloma patients with associated amyloidosis needs to be answered in a prospective, randomized study. On the other hand, it appears logical and tempting to take such patients directly to stem cell transplantation. If due to a high tumor burden it is necessary to administer cytotoxic agents, cardiotoxic (Adriamycin), neurotoxic (vincristine) and nephrotoxic agents should not be used. Finally, we caution that novel agents commonly used as frontline therapy for multiple myeloma (like thalidomide) can lead to life threatening bradycardia in cardiac amyloidosis patients and neurotoxicity can be exacerbated with drugs such as thalidomide or bortezomib. A summary of our recommen-

dations regarding induction therapy in myeloma-associated AL amyloidosis are outlined in Table 6.

Melphalan conditioning in myeloma-associated AL amyloidosis

The high TRM reported with early autograft studies in AL amyloidosis rapidly lead to the proposal of patient selection criteria (Table 4) and dose adaptation of high dose melphalan.⁶ The implementation of these criteria resulted in a better selection of patients eligible for transplantation and lead to a significant reduction in TRM. Few data are available regarding the optimal conditioning regimen for myeloma patients with coexisting amyloidosis as these patients are almost universally excluded from clinical trials. Two studies have shed some light on the outcomes of such patients. In a phase II study by Perz *et al.*,³³ eight of 28 patients with AL amyloidosis undergoing autologous stem cell transplantation met the criteria for multiple myeloma. Dominant organ amyloid involvement among these patients included renal (3/8; median serum creatinine 103 μ mol/l), cardiac (1/8), gastrointestinal/hepatic (2/8) and soft tissue (2/8). All patients received melphalan conditioning at 200 mg/m². Two patients died within 100 days of high dose melphalan (25% TRM) and the median survival was 39 months from autograft (range 0.3–68 months).³³ Although Desikan *et al.*³ noted no difference in survival parameters after autotransplant when ‘occult’ amyloidosis was detected in myeloma patients, the OS of patients with ‘symptomatic’ organ involvement appeared to be shorter compared to those with occult or no amyloid involvement (38 vs 59 and 66 months, respectively).³

These limited results suggest that autotransplant should not be withheld from myeloma patients with coexisting AL amyloidosis merely because of the presence of amyloid organ damage. Early recognition of the presence of amyloid organ dysfunction in myeloma patients is, however, crucial. Adoption of the selection criteria and melphalan dose-adjustment currently in use for AL amyloidosis will help reduce the TRM and preserve the therapeutic benefits of such approach for this subset of myeloma patients. Future studies will be needed to determine whether new prognostic factors such NT-proBNP and cardiac troponins will be validated in myeloma-associated AL amyloidosis.

Table 6 Summary of our recommendations for the treatment of patients with myeloma – associated AL amyloidosis

Induction	Consider proceeding to stem cell transplant directly without induction, in particular if <10% plasma cells in bone marrow If required, short course of pulse dexamethasone in induction is optimal Avoid cardiotoxic, neurotoxic and nephrotoxic drugs (Adriamycin, vincristine, thalidomide, bortezomib) Avoid long-duration induction regimens, do not wait for maximal response or CR
High-dose therapy	Melphalan dose adjustment according to risk group Need for multidisciplinary approach (cardiac, renal, neurologic)

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