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REVIEW

Current status of hematopoietic cell transplantation in the treatment of systemic amyloid light-chain amyloidosis

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Systemic amyloid light-chain (AL) amyloidosis is a protein conformation disorder caused by clonal plasma cell dyscrasias. Symptoms result from fibrillar extracellular deposits in various tissues. The deposits disrupt organ function and ultimately lead to death. The prognosis is poor and depends mostly on the severity of cardiac involvement. The treatment is derived from the therapy of multiple myeloma with the main goal being to reach a complete hematological remission (CR). High-dose melphalan (HDM) and autologous hematopoietic cell transplantation can induce CR rates in about 40%. The main concern was the high transplant-related mortality of up to 40% due to organ dysfunction, which could be reduced to <12% by careful patient selection in experienced centers. However, >50% of patients in CR survive longer than 10 years, suggesting that HDM has the potential to change the natural course of the disease. As there is evidence that 'graft-versus-plasma-cell-dyscrasia' effects are active in AL amyloidosis, allogeneic hematopoietic cell transplantation might be an option for younger patients with preserved organ functions who have relapsed after HDM.
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Introduction

Systemic amyloid light-chain (AL) amyloidosis is a rare protein folding disease with an incidence of about 8–12 newly diagnosed patients per million inhabitants in the USA.[1] It is a monoclonal B-cell disorder (mostly plasma cell dyscrasia) characterized by the accumulation of monoclonal light chain fragments, which have undergone a conformational transformation and deposit as amyloid fibrils in different tissues. The heart, kidney, peripheral nerves, liver and gut are the most frequently affected organs. Although the burden of the aberrant plasma cell clone in the BM is generally low, the sustained accumulation of amyloid protein leads to progressive and severe end organ failure and thereby death. The most important determinant of clinical outcome (among various prognostic factors, Table 1) is the extent of cardiac involvement,[2] which can be sensitively and reliably measured using the cardiac biomarkers cardiac troponin T and N-terminal prohormone of brain natriuretic peptide.[3,4] Evaluation of the amount of the involved (amyloidogenic)-free light chain (iFLC) in the serum is a very useful tool for the assessment of the underlying monoclonal gammopathy. The iFLC concentration reflects the expansion of the aberrant clone and to some extent the severity of organ involvement.[5,6] Whether cytogenetic aberrations of the plasma cell clone influence prognosis, like they do in patients with multiple myeloma (MM),[7] or predict response to different chemotherapies has to be evaluated in the future.[8,9]

Successful treatment of MM with high-dose melphalan (HDM) and autologous hematopoietic cell transplantation (auto-HCT) provided the rationale to establish this approach for selected AL amyloidosis patients, but only about 25% of newly diagnosed patients are eligible for HDM. Allogeneic-HCT (allo-HCT) is a new therapeutic option for younger patients who have relapsed after HDM and have preserved organ functions.[10]

HCT in AL amyloidosis was reviewed in this journal 10 years ago.[11,12] Since then, a number of new trials and developments have broadened the therapeutic spectrum for this disease, which continues to be associated with a dismal prognosis. Because AL amyloidosis is a very rare disease, randomized trials are sparse. Therefore, the following statements and recommendations are mostly based on the results from retrospective analyses and uncontrolled phase II trials, own experience and expert opinions. Unfortunately, there is no consensus as to whether the response after therapy should be reported as 'intention-to-treat' (then patients who die before first evaluation of response are classified as treatment failure, which reflects toxicity and efficacy of the treatment but strongly depends on the mix of the patient population) or only in 'evaluable'

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Table 1 Clinical determinants before start of therapy associated with reduced OS of AL patients

Prognostic factor	*Influence on outcome*	*References*
TNT/TNI NT-ProBNP/BNP	Mayo score (TNT $>0.035\,\mu g/L$ and NT-ProBNP $>332\,ng/L$)	3,81
Echocardiography	Reduced ejection fraction Abnormal strain rate Diastolic relaxation abnormality	82–84
Free light-chain level	Increased dFLC ($\kappa >29.4\,mg/L$, $\lambda >18.2\,mg/L$)	85
Uric acid level	UA levels greater than 8 mg/dL	86
No. of involved organs	Increased risk for TRM if more than two organs involved	87

Abbreviations: AL = amyloid light-chain; BNP = brain natriuretic peptide; dFLC = involved-uninvolved free light chain; FLC = free light chain; NT-ProBNP = N-terminal prohormone of brain natriuretic peptide; TNI = troponin 1; TNT = troponin T; TRM = treatment-related mortality; UA = uric acid.

patients (which gives 'higher' response rates and reflects mainly the efficacy of the therapy). Additionally, progression-free survival or time-to-treatment failure is not routinely reported and uniform definitions of 'progression' (hematological and/or organ progression) and treatment failure (for example, start of new chemotherapy in nonresponding patients before hematological progression occurs) are lacking. This, of course, compromises the comparability of clinical results.[13,14]

What is the evidence to support treatment with HDM in AL amyloidosis?

The first series of HDM treatment was published in 1996 by Martha Skinner and coworkers from Boston.[15] As proof of principle, many groups subsequently showed that the eradication of the plasma cell clone (CR) leads to improved organ functions (Table 2) (Consensus Criteria for hematological and organ response (OR) in Gertz *et al.*[16]). More than 2000 patients have been transplanted worldwide. The European Blood and Marrow Transplantation Society (EBMT) has registered over 1300 autologous and 27 allogeneic transplantations in AL amyloidosis since 2000 (Figure 1) and has published recommendations for transplant indications in AL amyloidosis.[17,18] Nowadays, there is a growing number of other chemotherapy options for AL amyloidosis having also the potential to induce complete suppression of the plasma cell clone.[19] This raises the question about the current role of HDM in AL amyloidosis.

What arguments support HDM?

First, CR rates after HDM are higher than after non-HDM therapies (Tables 2 and 3) and it is known that this is the most important factor for long-term survival of AL amyloidosis patients.[20] Second, relapse rate seems to be lower and the response duration appears to be much longer than in M-dex-treated patients (SO Schonland *et al.*, unpublished data). Third, a case–control study suggested superior survival over standard treatment approaches.[21] Furthermore, an improvement in quality of life[22] and long-term survival[20,23,24] could be demonstrated after HDM. The greatest obstacle is treatment-related mortality (TRM), which could substantially be reduced in experienced centers in recent years.[25,26]

There is only one randomized trial[27] in which 100 patients were randomly assigned to receive HDM or M-dex, which is considered to be the standard treatment for patients not eligible for auto-HCT. The outcome of the HDM group was inferior with a median overall survival (OS) of 22 months compared with 57 months ($P = 0.04$). However, there are several critical points to be discussed.[28–31] First, only 37/50 patients received the planned treatment in the HDM arm. Second, patients with severe cardiac involvement (New York Heart Association III and IV) were included leading to a very high TRM of 24%. Furthermore, the melphalan dosage was reduced in 10 patients to $140\,mg/m^2$ that is associated with lower hematological remission (HR) rates.[32] This study raised a huge discussion in the amyloidosis community, but most centers concluded that it should not lead to ban HDM for AL amyloidosis patients. A systematic review to compare mortality, efficacy and OS after auto-HCT or conventional chemotherapy (M-dex or -prednisone, VCR-adriamycin-dex (VAD)) was published in 2009.[33] Although the authors conclusions showed that auto-HCT was not superior to conventional chemotherapy, they did note that the quality of evidence was on a low level. Furthermore, their approach and analytical techniques were heavily questioned.[34] Taken together, these studies highlight the necessity of using vigorous eligibility criteria and profound AL-specific center experience to avoid inacceptable TRM and to harmonize clinical endpoints in AL amyloidosis to allow a better comparability of treatment results.

Recently, the new anti-myeloma drugs as bortezomib, thalidomide and lenalidomide have also been introduced in AL amyloidosis therapy. There are only a few fully published reports about administration as single drug or in combination with dex or cytostatic agents, mostly used as second- or third-line treatment (Table 3). Though promising results regarding HR and OR have been described, data about remission duration and long-term survival are lacking. A future application could be the combination with HDM to further enhance CR rates.

In summary, melphalan is effective in AL amyloidosis, and there is evidence that dose-intensification of melphalan results in superior plasma cell disease control, whereas the role of the new myeloma-specific drugs needs to be established. Therefore, HDM continues to have an important role for eligible patients in most Amyloidosis centers. A second phase III trial of the Mayo Clinic comparing HDM and M-dex has started in 2005 and will better define the role of HDM (NCT00477971; http://www.clinicaltrials.gov).

Table 2 Results of single- and multi-centre studies of HDM and auto-HCT in patients with AL amyloidosis

Reference	*Recruitment*	*Pts transplanted*	*Melphalan dosage*	*TRM (%)*	*Median follow-up (months)*	*HR CR OR (no pts./eligible pts. (%))*	*OS 1 year (%)*	*OS>2 year (%)*
Single-centre clinical trials								
Lachmann *et al.*[88]	NA	55	NA	22	20	NA	NA	NA
Gertz *et al.*[89]	2004–	270	⩽200	11		177/213 (83%) 86/213 (40%) NA	NA	NA
Mollee *et al.*[90]	1996–2001	20	140–200	35	18 for pts alive	10/18 (56%) 5/18 (28%) NA	NA	56 (3 years)
Perz *et al.*[39]	1998–2003	24	100–200	13	31	13/21 (62%) 11/21 (52%) NA	84	84
Skinner *et al.*[91]	1994–2002	277	100–200	13	NA	NA 73/181 (40%) 80/181 (44%)	79	47 (5 years)
Perfetti *et al.*[24]	1995–2002	22	100–200	14	47	12/18 (67%) 8/18 (44%) 10/18 (56%)	80	55 (5 years)
Cohen *et al.*[48]	2002–2005	44		2	31 for pts alive	32/41 (78%) 16/41 (39%) 20/44 (44%)	91	84 (2 years)
Mangatter *et al.*[41]	1998–2007	100	100–200	3	28	75/95 (79%) 42/95 (44%) 40/92 (43%)	88	70 (5 years)
Multi-centre clinical trials								
Moreau *et al.*[92]	1993–1997	21	140–200	43	14	NA 3/12 (25%) 10/12 (83%)	NA	57 (4 years)
Goodman *et al.*[93]	1994–2004	92	NA	23	NA	34/51 (67%) 18/51 (35%) NA (48%)	NA	NA
Vesole *et al.*[26]	1995–2001	107	>130	27		34/78 (44%) 17/78 (22%) NA	66	56
Gertz *et al.*[94]	1998–2000	28	200	14	30 for pts alive	NA NA 18/24 (75%)	NA	62 (3 years)
Jaccard *et al.*[27]	2000–2005	37	140–200	24	36	18/27 (67%) 11 27 (41%) 13/29 (45%)		58 (3 years)
Hazenberg *et al.*[38]	2000–2006	46	NA	11	NA	NA NA NA (26%)		90 (3 years)

Abbreviations: AL = amyloid light-chain; auto-HCT = autologous hematopoietic cell transplantation; HDM = high-dose melphalan; HR = hematological remission; pts = patients; OS = overall survival; TRM = transplant-related mortality.
HR, CR and OR rates were calculated in patients eligible for response. CR rate after HDM was 38% (290/755 pts). To calculate the intention-to treat results you might use numbers of patients being transplanted in column 3.

In the following paragraphs we review the current knowledge about specific issues of auto-HCT and summarize the sparse data about allo-HCT.

Which patients are eligible for HDM and auto-HCT?

Patient selection is crucial as TRM is an important issue in AL amyloidosis patients. Different criteria of eligibility have been used in the published reports and in our center (Table 4). Eligibility itself is a positive prognostic factor.[35] Currently, the cardiac biomarkers have an important role in deciding whether HDM will be recommended to the patient.[3] In most of the patients HDM will be performed as first-line therapy.

Résumé: patients with advanced amyloidosis and cardiac disease (depending on performance status, New York Heart Association stage or elevated cardiac biomarkers) are not candidates for HDM.

Should induction chemotherapy be used before HDM?

The main advantage of induction treatment (IT) is the reduction of light chain load with consecutive chance for organ function stabilization already prior to HDM.

Furthermore, conventional dose chemotherapy might be a 'test' for the capacity to withstand HDM. The overall goal is to increase CR rates post HDM that is also associated with long-term OS in patients with MM.[36] Disadvantages of this approach are possible side effects, risk of worsening of organ functions and consecutively delay of HDM.

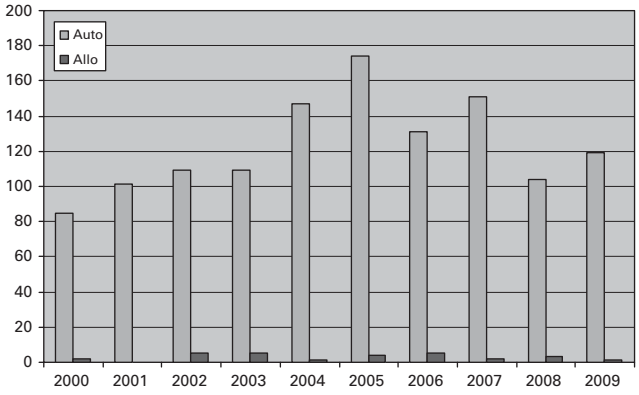

Figure 1 Overview of AL amyloidosis transplants 2000–2009 registered within the EBMT.

IT has been tested in a randomized trial in 100 patients by the Boston group.[37] They applied two cycles of melphalan-prednisone before HDM and compared this to HDM without IT. No advantage in OS, hematological and clinical responses was observed for the melphalan-prednisone group. The HOVON applied three cycles of VAD before HDM in a prospective trial in 69 patients[38] and observed prolonged survival in patients who reached HDM. We have performed two prospective trials at our institution,[39,40] the first with VAD, the second using high-dose dex. We could show that achievement of HR before HDM is associated with a higher probability for CR after HDM and a prolonged survival.[41] However, toxicity was remarkable with TRM up to 10%. VAD will no longer be used for AL amyloidosis patients at our institution because of the high risk of cardiac toxicity. An ideal drug for IT would lead to a fast and deep HR with a good toxicity profile. Therefore, a randomized trial comparing high-dose dex with Bortezomib-dex as IT before HDM is planned in the Netherlands, Belgium and Germany.

Table 3 Results of conventional chemotherapy in AL amyloidosis

Reference	*No. of pts*	*Recruitment Median follow-up*	*Median age (years)*	*Treatment*	*HR CR OR*	*Median OS (months) # death within 3 months, % of pts*
Palladini *et al.*[95]	46[a]	1999–2002 20 months (living pts)	62	M-dex	NA (67%) NA (33%) NA (48%)	Not reached 4%
Jaccard *et al.*[27]	50[a]	2000–2005 NA	59	M-dex	26/38 (68%) 12/38 (32%) 17/44 (39%)	57 10%
Lebovic *et al.*[96]	40[a]	2004–2007 NA	67	M-dex	23/40 (58%) 5/40 (13%) NA	10.5 23%
Dietrich *et al.*[97]	61[a]	2004–2007 27 months	65	M-dex i.v.	27/41(66%) 7/41 (17%) 15/41 (37%)	17.5 28%
Wechalekar *et al.*[98]	75[b]	2000–2005 22 months	60	CTD	46/65 (74%) 14/65 (21%) 16/60 (27%)	Not reached 4%
Kastritis *et al.*[68]	94[c]	NA 10 months for untreated pts	62	B-dex	67/93 (72%) 23/93 (25%) 29/94 (30%)	Not reached 3%
Reece *et al.*[69]	31	2005–2007 NA	59	B	15/29 (52%) 6/29 (21%) NA	NA
Sanchorawala *et al.*[99]	34	2004–2006 NA	65	L-dex	16/24 (67%) 7/24 (29%) 6/17 (25%)	NA
Dispenzieri *et al.*[100]	22[d]	2004–2005 17 months	62	L (dex)	9/22 (41%) (NA) 5/22 (23%)	NA
Moreau *et al.*[101]	26[a]	2008–2009 19 months	57	L-M-dex	15 /26 (58%) 6/26 (23%) 13/26 (50%)	Not reached 0%

Abbreviations: AL = amyloid light-chain; B = Bortezomib; CTD = cyclophosphamide, thalidomide, dexamethasone; HR = haematological remission; L = lenalidomide; M = melphalan; na = not available; OR = organ response; pts = patients; dex = dexamethasone.
HR, CR and OR rates are calculated in eligible patients. CR rate were 22% (80/356 patients). To calculate the intention-to treat results you might use numbers of patients being transplanted in column 2.
[a]first-line treatment.
[b]31 pts. first line.
[c]18 pts. first line.
[d]Nine pts. first line.

Table 4 Exclusion criteria for HDM in eight centers and study groups worldwide

Center	*Exclusion criteria for HDM*
Amyloidosis Center Boston[91]	>70 years, >NYHA II, PS >2, systolic blood pressure <90 mm Hg, symptomatic pleural effusions, EF ⩽40%
Amyloidosis Program Mayo Clinic[89]	>70 years, PS ⩾2, cTNT >0.06 ng/mL, Crea-cl <30 mL/min (unless on chronic dialysis), NYHA >II, >2 organs significantly involved
Amyloidosis Center Pavia[102]	>2 organs involved, severe cardiac involvement, creatinine >2 mg/dL, abnormal respiratory function test, >65 years
Memorial Sloan Kettering NY[96]	⩾60 years, ⩾3 organs involved, advanced cardiac disease
HOVON Study Group[38]	PS> , NYHA>III, EF ⩽45%, other severe diseases
French Study group[101]	Inadequate organ function, elevated NT-ProBNP and TNT
National Amyloidosis Center London (A Wechalekar, personal communication)	>2 organs, ECOG >1, eGFR ⩽50 mL/min, significant cardiac involvement, autonomic neuropathy or gastrointestinal involvement, TNT ⩾0.06.
Amyloidosis Center Heidelberg *et al*.[41]	>70 years, >NYHA II, PS >2, systolic blood pressure <90 mm Hg, symptomatic pleural effusions, factor × deficiency <10%. Since 2009: Crea-cl <30 mL/min (unless on chronic dialysis)

Abbreviations: Crea-cl = creatinine clearance; cTNT = cardiac troponin T; ECOG = Eastern Cooperative Oncology Group; EF = ejection fraction; eGFR = epidermal growth factor receptor; GFR = glomerular filtration rate; HDM = high-dose melphalan; NT-ProBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; PS = performance score.

Résumé: the use of IT has to be further evaluated in prospective clinical trials. IT with Bortezomib-dex might be a beneficial strategy to improve outcome after HDM. Melphalan-prednisone or VAD should no longer be used as IT.

What is the safest and most effective way for hematopoietic cell mobilization (HCM)?

HCM can be performed with or without chemotherapy. Most centers use granulocyte-CSF (G-CSF) alone. However, the risk for severe complications is remarkable with or without the application of chemotherapy compared with MM. In a large monocentric analysis 16% of patients who began HCM with G-CSF did not proceed to HDM: 10/35 patients died and 25 patients did not complete collection because of complications such as hypotension, hypoxemia, gastrointestinal bleeding or decline of performance status.[42] In another study HCM was performed with G-CSF alone or in combination with CY (33 patients in each group).[43] One patient died of respiratory distress syndrome from growth factor application. Surprisingly, in patients receiving CY significantly more leukaphereses (median of 3 vs 2) were required to achieve $>2\times10^6$ CD34+ cells/kg body weight. Sequential GM-CSF + G-CSF or G-CSF was used for HCM in 30 AL amyloidosis patients.[44] One patient died at the initiation of growth factors due to gastrointestinal bleeding. A further five patients had severe complications. The number of hematopoietic cells collected depended on dosage of prior melphalan exposure. It could be shown that in poor mobilizers (for example, in melphalan exposed patients) the addition of AMD 3100 (plerixafor) is effective to collect the requested number of hematopoietic cells.[45]

We have evaluated the data of HCM in 110 AL amyloidosis patients transplanted at our institution, 99 patients received chemotherapy (mostly CY based) plus G-CSF for HCM.[46] No patient died of HCM treatment. The efficacy was high with a median of 8×10^6 CD34+ cells/kg body weight (range, 0–46) collected cells with a median of one leukapheresis procedure. Previous melphalan exposure and G-CSF mobilization alone were significantly associated with a reduced hematopoietic cell yield ($P<0.01$ each).

Résumé: melphalan treatment before mobilization should be avoided. G-CSF is still the standard for HCM in AL amyloidosis patients. However, the application of mobilization chemotherapy plus G-CSF could be advantageous to further enhance clone control and to collect more hematopoietic cells.

Should AL amyloidosis patients receive a tandem transplant as in MM or other consolidation treatments to further improve HR?

A small series of tandem HDM was published by the Boston group in 2007.[47] Sixty-two patients were enrolled in the study, 53 patients received a first HDM. Twenty-seven patients achieved a CR 6 months after the first HDM cycle. Seventeen patients without CR were treated with a second HDM cycle of whom five achieved a CR. Overall, CR rate of the evaluable patients was 67%. It was concluded that tandem cycles can improve HR. Another approach was used by Comenzo and coworkers. They applied thalidomide (thal) and dex as adjuvant treatment after risk adapted HDM within a phase II trial.[48] Forty-five newly diagnosed patients were included. Thirty-one patients with persistent clonal disease 3 months after HDM received thal/dex, or dex alone. Sixteen patients completed the planned 9-month schedule; in 13 patients an improvement of HR was observed. The overall HR was 71% (36% CR), the OR rate was 44%. Two-year survival was 84%. In a consecutive trial bortezomib/dex was administered to 15 patients following HDM.[49] HR improved in 7 out of 8 patients. Overall HR was 92% (67% CR), OR was 50%.

Résumé: current data are not sufficient to recommend tandem transplants in AL amyloidosis patients. Consolidation treatment with new drugs is promising, but this should be validated in further clinical trials.

Can HDM be safely given in patients with end-stage renal disease (ESRD)?

HDM has been performed in AL amyloidosis patients with ESRD. Casserly *et al*.[50] treated 15 patients with ESRD with 70–200 mg/m^2 melphalan. TRM was 13%, HR was achieved

in 53%, 5 patients with CR received kidney transplants later on. There was a trend toward increased severity of mucositis and transfusion requirements. In a recent analysis[51] 32 patients were reported with a TRM of 6%. CR rate was 70% in patients eligible 1 year after HDM. Median survival was 5.3 years (6.1 years for patients in CR).

Résumé: HDM is feasible in patients with ESRD and might offer the opportunity to perform kidney transplantation if the patient achieves sustained CR. The optimal melphalan dosage in AL amyloidosis patients with ESRD is not known. We apply 100 mg/m^2 (divided on 2 consecutive days, dialysis on days -3 and -1 and $+1$).

Which factors influence OS after HDM? Is AL amyloidosis a curable disease?

Post-transplant factors have a strong influence on OS after HDM. The achievement of CR of the gammopathy[16] is the most important factor for long-term survival of AL amyloidosis patients. Three studies have shown that CR patients can survive >10 years[20,23,24] and the probability of achieving a CR after HDM depends on the melphalan dosage.[32] OS is depending on the degree of free light chain reduction; a reduction of $>90\%$ is also associated with longer survival.[52] In another study, percent FLC reduction did not predict OS, but normalization of the FLC achieved after HDM did.[6] Finally, in a large series of AL amyloidosis patients (including 73 HDM treatments) a 30% and >300 ng/L decrease of N-terminal prohormone of brain natriuretic peptide went along with significant prolonged OS.[53]

Résumé: achievement of HR is the most important factor for OS. A cure of AL amyloidosis requires sustained CR of the underlying gammopathy (for example, >5 years). However, we have observed relapse even 10 years after HDM. Data about hematological progression-free survival are mostly missing in the published studies. Therefore, it remains unclear how many patients are 'cured' after HDM.

How can TRM and severe organ complications after HDM be reduced?

Because of the pre-existing organ damage TRM of auto-HCT is much higher in AL than in other hematological malignancies. The degree of TRM depends on patient selection. Patients with cardiac involvement are at the highest risk of dying from cardiac events during sepsis or pneumonia. In recent years, it has been possible to reduce TRM to below 12% in experienced centers.[25,41] At the same time data have been accumulating, that in centers with low numbers of AL amyloidosis transplants TRM might be higher than in experienced centers.[26,27]

Renal toxicity is also remarkable[54,55] especially in patients with kidney involvement, high proteinuria and low serum albumin levels. In a retrospective trial at the Mayo Clinic 80 AL amyloidosis patients were studied.[54] Acute renal insufficiency was observed in about 19% of patients. The timing of renal injury suggested that melphalan was one causative agent.

Dose adjustment of melphalan has been recommended in MM patients with reduced creatinine clearance.[56,57] Many Amyloidosis Transplant centers exclude patients with renal failure from HDM (Table 4). The optimal dosage of HDM in AL patients with reduced creatinine clearance is unknown. In the past, we reduced the dosage of HDM to 140 mg/m^2 in patients with a creatinine clearance <30 mL/min. Since 2009 we exclude these patients from HDM until they are on chronic hemodialysis.

Résumé: in our view, HDM should only be performed in centers with considerable experience with AL amyloidosis patients. Careful patient selection is crucial as pointed out above.

Which supportive therapy is necessary during high-dose therapy?

Supportive treatment has a special role in patients with AL amyloidosis because of the pre-existing organ damage. This includes nutrition, volume status, nephrotic syndrome, albumin deficiency, coagulation impairment and cardiac arrhythmias. A close cooperation with nephrologists and cardiologists is mandatory.

In patients with gastrointestinal involvement or coagulation impairment maintenance of platelet values >20–$50\,000/\mu$L to prevent severe bleedings should be considered.[18,58] G-CSF administration after HDM is a standard of care in the US. However, it has recently been shown that withholding growth factor therapy after HDM is feasible.[59] In a prospective trial patients received oral cryotherapy during and 15 min before and after HDM to reduce the incidence and severity of mucositis.[51]

Cardiac arrhythmias are very common in patients with amyloidosis. The benefit of telemetric monitoring during HDM has investigated in a recent analysis of 24 patients.[60] Three patients had received pacemaker or defibrillator before HDM. After HDM, 20 patients required intervention for cardiac arrhythmias, 3 had life-threatening episodes. A decreased cardiac output was strongly associated with significant arrhythmias. Arrhythmias were treated with antiarrhythmic drugs or change of the β-blocker dosage. In one patient a defibrillator was implanted. Four patients died within 3 months after HDM, two of them during telemetry monitoring. Our center has performed prophylactic implantation of cardioverter-defibrillator in 19 AL patients.[61] Two patients with ventricular tachyarrhythmias were treated successfully, but six patients died of electro-mechanic dissociation, which is a common cause of sudden cardiac death in AL patients. Whether prophylactic implantation of defibrillators reduces the rate of cardiac complications during HDM or afterward has still to be determined.

Résumé: interdisciplinary care (hematology, cardiology and nephrology) is essential for AL amyloidosis patients during HDM considering impaired organ functions.

Should auto-HCT also be done when a B-cell lymphoproliferative disorder is the underlying disease?

HDM and auto-HCT were rarely applied to those patients.[62,63] HR rate was 89% and OR rate 67%. TRM did not differ from patients compared with those with a plasma cell dyscrasia as the underlying disorder.

Non-Hodgkin lymphoma-directed conditioning using BEAM was also used in two patients.[64]

Résumé: results of auto-HCT on AL amyloidosis in B-cell non-Hodgkin's lymphomas might be comparable to those in patients with monoclonal plasma cell disorders. However, the optimal type and dosage of conditioning is unknown. The kind of chemotherapy should probably be determined according to the relative lymphoid or plasmacytoid features of the neoplasm.

Is a different approach in patients with symptomatic MM and concomitant AL amyloidosis necessary?

The Boston group recently published 16 patients suffering from MM/AL with HDM.[65] Three patients died of TRM (two during stem cell mobilization). Melphalan dosage was reduced in 44% of patients. CR rate at 6 months was 25% and relapse rate after 1 year was 60%. Median OS after HDM was 54 months.

Résumé: MM patients with concomitant AL amyloidosis and significant organ involvement should be treated like AL amyloidosis patients (careful patient selection, only short IT (no VAD), detailed organ investigations before HDM, consider dose reduction of melphalan and intensive supportive care during HDM).[66]

How should AL amyloidosis patients be followed after HDM and treated after relapse?

After HDM and auto-HCT the monoclonal gammopathy and organ involvement should be closely evaluated, especially in patients being not in CR. Those patients have an increased risk for organ progression and the need of further chemotherapy. Various types of treatment have been used to treat patients after HCT. A prospective study using HDM for treatment of relapse has recently been published.[67] HDM was given at a dosage of 140–200 mg/m^2. They observed no TRM or death during the first year after HDM, but significant grade III/IV toxicity. Four out of the 11 patients achieved CR (36%), two relapsed after 2 and 3 years, respectively. Three out of four patients with PR progressed at a median of 3 years. Currently, the new drugs like bortezomib or lenalidomide are successfully being used to induce second remission of gammopathy.[68–70] In patients with amyloid neuropathy lenalidomide/dexa should be given first. In young patients allo-HCT can be discussed.[10]

Résumé: the indication to initiate a new therapy depends on several individual factors such as age, cardiac and renal function and time since HDM. The goal is to avoid organ progression. A second HDM course cannot be recommended based on the available data. Bortezomib/dexa or lenalidomide/dexa should be used, but in reduced dosages compared with MM patients.

Are there indications for organ transplantation prior or post HDM?

For patients below 60 years with isolated and advanced cardiac amyloidosis (survival about 3.5 months) urgent cardiac transplantation followed by HDM is a new treatment option with encouraging results.[71–73] Kidney transplantation may be offered to patients with ESRD achieving CR after HDM; interestingly, no transplant failed because of recurrent amyloid deposits.[74] Another approach was published by the Mayo Clinic, where they transplanted living donor renal allografts followed by full dose HDM.[75] In an expanded cohort of 19 patients, 79% were alive after a median follow-up of 41 months.[76]

Résumé: organ transplantation is a therapeutic option in selected patients with kidney or cardiac failure. Heart transplantation may render otherwise ineligible patients with AL amyloidosis eligible for auto-HCT.

Is there a role for allo-HCT in AL amyloidosis?

Anecdotal reports of successful BMTs for AL were published in the early nineties.[77,78] In the following years, further cases using peripheral blood hematopoietic cells were published. The largest retrospective analysis on allo-HCT for AL amyloidosis was performed by the EBMT in 2006.[10] Nineteen patients were analyzed in detail, four of them had syngeneic donors. Seven patients received myeloablative and eight reduced-intensity-conditioning. A total of 40% of patients died of TRM. Long-term survival and sustained CR was achieved in seven patients and was associated with chronic graft-versus-host disease in the majority of them. Donor lymphocyte infusion has been successfully performed in a few patients with AL amyloidosis,[79] thereby demonstrating a potent 'graft-versus-plasma cell dyscrasia' effect. In patients with MM, relapse is the main problem after allo-HCT. The immunological effect of the transplant might be better in AL amyloidosis because the tumor burden is low and there are fewer chromosomal aberrations compared with MM.[9]

The EBMT has initiated a non-interventional prospective study for patients with AL amyloidosis undergoing allo-HCT. Details can be found on the EBMT website (http://www.ebmt.org). The main goal is the reduction of TRM, which can be achieved using reduced-intensity-conditioning (for example, 2 Gy TBI and fludarabine).

Résumé: allo-HCT after reduced-intensity-conditioning should be discussed as a treatment option for relapse after auto-HCT in patients <60 years with preserved organ functions and a HLA-identical donor. It might be a curative treatment for highly selected patients.

Conclusion and perspectives

In specialized centers, HDM with auto-HCT is still the treatment of choice for patients with AL amyloidosis who fulfill specific clinical criteria. Retrospective analyses show that $>50\%$ of AL amyloidosis patients who achieve CR survive longer than 10 years. Furthermore, it is mandatory to measure FLC levels and cardiac biomarkers at diagnosis, prior and regularly post HDM, to estimate the survival prognosis of an individual AL amyloidosis patient. Additionally, it is important not to miss the optimal time

point of second-line treatment. HR criteria have been elaborated recently to better define the prognosis of patients not being in CR.[53] In this context, a clear definition of progression-free survival is necessary to facilitate comparison of clinical trials in AL amyloidosis. The combination of the new anti-myeloma drugs with HDM might lead to an increase of CR rates and improvement of OS. Prospective multicenter studies and international collaboration are necessary to better define the significance of HDM and auto-HCT in patients with this rare disease.[80] The significance of allo-HCT in AL amyloidosis needs to be established. In the future, drugs which are either directed against amyloid conformation or which accelerate amyloid degradation might be added to or given post chemotherapy.

Conflict of interest

The authors declare no conflict of interest.

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