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GUIDELINE ARTICLE

Guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis: EHA-ISA working group guidelines

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ABSTRACT

AL amyloidosis is a systemic amyloidosis and is associated with an underlying plasma cell dyscrasia. High dose intravenous melphalan and autologous stem cell transplantation was developed for the treatment of AL amyloidosis in the early 1990s and was prompted by its success in multiple myeloma. This application has evolved significantly over the past three decades. These guidelines provide a comprehensive assessment of eligibility criteria, stem cell collection and mobilisation strategies and regimens, risk-adapted melphalan dosing, role for induction and consolidation therapies, specific supportive care management, long-term outcome with respect to survival, haematologic response and relapse and organ responses following stem cell transplantation. These guidelines are developed by the experts in the field on behalf of the stem cell transplant working group of the International Society of Amyloidosis (ISA) and European Haematology Association (EHA).

Abbreviations: BMPC: bone marrow plasmacytosis; CR: haematologic complete response; GCSF: granulocyte colony stimulating factor; HDM/SCT: high dose melphalan and stem cell transplantation; HT: heart transplant; TRM: treatment realted mortality; VGPR: very good partial response

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Introduction

AL amyloidosis is a systemic amyloidosis associated with a low level of plasma cell or B-cell lymphoproliferative disorder. Monoclonal immunoglobulins or free light chains misfold, aggregate and form amyloid deposits which lead to organ dysfunction [1]. Current treatment are focusing on eliminating the source of precursor amyloidogenic light chains with therapies directed against plasma cell dyscrasia. High dose intravenous melphalan and autologous stem cell transplantation (HDM/SCT) was developed for the treatment of AL amyloidosis in the early 1990s, prompted by its success in multiple myeloma [2]. Initial objectives of the clinical trials of HDM/SCT in AL amyloidosis were to assess tolerability of this intensive treatment in patients with multiorgan involvement, to assess haematologic response by elimination of the plasma cell dyscrasia and finally to assess if haematologic response led to reversal of organ dysfunction and improvement in survival. This application has evolved significantly over the past three decades [3,4]. These guidelines provide a comprehensive assessment of eligibility criteria, stem cell collection and mobilisation strategies, risk-adapted melphalan dosing, role for induction and consolidation therapies and haematologic response and organ responses following stem cell transplantation. In addition, these guidelines also provide supportive care measures during stem cell transplantation for better outcomes. Continued efforts to refine patient selection and management and incorporate novel anti-plasma cell agents in combination or sequentially to further improve outcomes in AL amyloidosis are needed. Role of stem cell transplantation in AL amyloidosis is being questioned with advent of novel regimens incorporating monoclonal antibodies that lead to high haematologic and organ responses.

Due to its rarity and lack of many randomised clinical trials, the guidelines presented here are based on expert opinions of the panel members.

Eligibility criteria

Selection of patients for high dose chemotherapy and stem cell transplantation (SCT) is crucial as treatment related morbidity and mortality is significantly higher when compared to multiple myeloma due to organ dysfunction, organ failure and poor performance status. Treatment related

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Table 1. Risk-adapted melphalan dosing prior to SCT.

	MEL 200[a]	Multidisciplinary discussion MEL 200 vs bortezomib based regimen	MEL 140
Age (years)	≤65	66–69	–
Cardiac stage	I or II	II or III	–
eGFR (mL/min/m^2)	>50	30–50	<30[b]

[a]Patient must meet all criteria to receive MEL 200.
[b]Increased risk of AKI and ESRD during peri-SCT period, can consider if on a stable chronic dialysis schedule.

mortality has decreased significantly over several decades from 20% to <5% due to careful patient selection [5,6], patient selection driven predominantly by cardiac biomarkers to not treat those with advanced cardiac involvement with SCT [7], availability of effective non-SCT therapies [8] and better supportive care.

Eligibility criteria vary for centres depending on the experience, local policies and standard operating procedures, however, only 20%–30% (or fewer) of newly diagnosed patients are eligible for this intensive treatment. "Deferred" eligibility is achievable if organ function significantly improves after induction chemotherapy.

Broad eligibility criteria for SCT in AL amyloidosis are as follows:

- Confirmed tissue diagnosis of amyloidosis and accurate typing proving AL amyloidosis
- Clear evidence of a clonal plasma cell dyscrasia
- Age >18 years and <70 years (Patients older than 70 years of age should be discussed in a multidisciplinary setting and evaluated for eligibility for SCT in a centre of excellence with experience)
- At least one major vital organ involvement (soft tissues involvement alone or amyloid deposition in bone marrow alone are not considered to be vital organ involvement)
- Left ventricular ejection fraction ≥40%, NYHA class < III
- Oxygen saturation 95% on room air, DLCO >50%
- Supine systolic blood pressure ≥90 mm Hg
- ECOG performance status score ≤2 unless limited by peripheral neuropathy.
- Direct Bilirubin <2 mg/dL
- NTproBNP <5,000 pg/mL
- Troponin I <0.1 ng/mL and Troponin T <60 ng/L and hs-Troponin T <75 ng/mL
- eGFR >30 mL/min/m^2 (Patients with eGFR <30 mL/min/m^2 and not yet on dialysis are at an increased risk of worsening of renal function during SCT [9], refer to Table 1 for melphalan dose or defer SCT)
- Patients on chronic and stable schedule of dialysis for ESRD should not be excluded if other eligibility criteria met [10]

Definite exclusions for SCT in AL amyloidosis are as follows:

- Symptomatic and/or medically refractory ventricular and atrial arrhythmias
- Symptomatic and/or medically refractory pleural effusions
- Uncompensated heart failure
- Orthostatic hypotension refractory to medical therapy
- Factor X deficiency with factor X level of <25% or/and evidence of active bleeding
- Extensive GI involvement with evidence of active GI bleeding or risk of bleeding

Recommendation: Careful patient selection is critical for the success of SCT in AL amyloidosis.

Induction therapy prior to SCT

Survival in AL amyloidosis is predicted by the depth and, in those with significant organ dysfunction, speed of haematologic response, as well as the duration of suppression of the underlying plasma cell clone. For those who can tolerate the procedure, SCT has been shown over a number of decades to achieve each of these: deep, rapid and durable responses. Historically, because of the underlying low burden of bone marrow plasma cells, initial debulking induction chemotherapy as used in multiple myeloma was not thought to be necessary. Induction therapy was also postulated to impair outcomes in few patients due to clinical deterioration of organ function during the induction phase making some patients ineligible for SCT.

This approach has been challenged by the development of novel agent induction treatment protocols. Several retrospective and prospective studies have demonstrated that bortezomib-based induction therapy is feasible and associated with high responses [11–15]. The only randomised study of SCT with or without bortezomib-based induction, conducted in patients with renal AL amyloidosis, reported superior haematologic responses and overall survival favouring the bortezomib induction arm [16]. Conflicting reports have been published on whether those with bone marrow plasmacytosis ≥10% benefit from induction, although these studies were not confined to those receiving bortezomib-based protocols [17,18]. Use of induction allows the option of deferral of SCT in the event of good clonal control or alternatively may lead to an organ response by the time the SCT is delivered, potentially increasing the proportion of patients becoming transplant eligible and decreasing the likelihood of transplant-related mortality or further organ damage.

The Dara-VCd (daratumumab, bortezomib, cyclophosphamide, dexamethasone) regimen further improves the speed and depth of haematologic response [8]. Such induction will become the preferred initial therapy for both pragmatic reasons, as chemotherapy can be commenced immediately, and due to therapeutic effectiveness. Whether consolidation with SCT will then optimise the duration of disease control as it does in multiple myeloma induced with the VCd regimen remains to be tested, particularly in those achieving complete haematologic response to induction therapy. The use of Dara-VCd induction before SCT has not been systematically studied, but several points can be

inferred from the ANDROMEDA study which was largely performed in the non-transplant setting. With Dara-VCd, the median time to complete haematologic response was 60 days and nearly all the dFLC reduction occurred by the end of cycle 4. In the prospective studies of bortezomib and dexamethasone, two to four cycles of induction were administered. As such, it would seem reasonable to deliver two to four cycles of Dara-VCd induction prior to planned SCT. For patients who achieve haematologic complete response after two to four cycles of induction therapy, consideration should be given to completing induction without SCT which could be delayed to the first suggestion of haematologic relapse. Although this recommendation lacks randomised clinical trial data support, panel members are in agreement with this approach.

Recommendation: Induction therapy with bortezomib based regimen ± daratumumab for 2–4 cycles should be considered if bone marrow plasmacytosis >10% and defer SCT if haematologic CR achieved with induction therapy.

Stem cell mobilisation and collection

Contrary to the common experience in multiple myeloma, deaths have been reported during mobilisation and leukapheresis of patients with AL amyloidosis who have cardiac or multiorgan involvement. Overall, the incidence of major complications, during stem cell mobilisation and collection is approximately 15%. Stem cell mobilisation is associated with unusual morbidity of hypotension, hypoxia, cardiac arrhythmia and fluid retention in AL amyloidosis. The risk for side effects is especially increased in patients who already have fluid retention due to nephrotic syndrome or congestive heart failure. The toxicity during mobilisation and collection have the potential to delay or hamper treatment with high-dose chemotherapy due to worsening of performance status or organ function. Some patients with advanced cardiac involvement and hypotension may benefit from inpatient cardiac monitoring and fluid management during stem cell mobilisation and collection [19,20].

The recommended target dose of CD34+ cells is $4–5 \times 10^6$ CD34+ cells/kg with a minimum of 2.5×10^6 CD34+ cells/kg [21]. Plerixafor, a CXCR4 receptor antagonist, as a stem cell mobilisation regimen along with abbreviated dose of G-CSF can be beneficial in patients with fluid overload to reduce the dose of G-CSF and hence the risk of capillary leak syndrome and also reduce the number of leukapheresis sessions needed for optimal stem cell collection yield [22,23]. Monitoring of patient weight, electrolytes, blood pressure, oxygen saturation and platelet counts before and after stem cell collection is recommended.

The recommended dose of G-CSF is 10–16 mcg/kg/day, either as a single dose or in two divided doses, 3–4 days prior to stem cell collection.Cyclophosphamide and G-CSF mobilisation may be utilised for stem cell mobilisation in patients with multiple myeloma associated AL amyloidosis as per institutional guidelines. Pre- and post-cyclophosphamide intravenous hydration should be used with extreme caution in patients with cardiac and renal involvement from AL amyloidosis. Use of mesna to prevent haemorrhagic cystitis is recommended with cyclophosphamide.

Recommendation: G-CSF at 10–16 mcg/kg/day, either as single or split dose and plerixafor (on demand or planned) for patients with cardiac involvement should be used for stem cell mobilisation. Close monitoring of electrolytes and volume status should be performed during stem cell collection.

Conditioning regimen

High dose melphalan is the standard conditioning regimen used prior to SCT in patients with plasma cell disorders and is associated with deep and durable responses in patients with AL amyloidosis. However, initial studies using full-intensity conditioning with melphalan 200 mg/m^2 in patients with AL amyloidosis reported high rates of treatment-related mortality (TRM) (~20%) which was particularly evident in patients with advanced age, congestive heart failure and/or multiorgan involvement. To reduce treatment-related complications, modified melphalan dosing (100–140 mg/m^2) has been used in patients who are at highest risk of morbidity and mortality from SCT [24,25]. While full-dose melphalan conditioning has been associated with improved outcomes, the patients who are eligible to receive melphalan at 200 mg/m^2 are a healthier population. Modified melphalan conditioning with melphalan at 140 mg/m^2 in patients who are ineligible for melphalan at full-dose is a possible treatment option associated with low TRM and prolonged OS, especially in patients who achieve a haematologic CR. It is important to note that bortezomib based treatment regimens can lead to haematologic responses similar to those achieved with modified melphalan dose and SCT, although there is no randomised clinical trial to assess this. However, in view of very effective regimens of bortezomib and daratumumab based regimens in achieving deep haematologic response, modified high dose melphalan may have a role in the second line or salvage setting rather than frontline approach.

Alternative conditioning approaches in AL amyloidosis have also been explored in clinical trials and these include incorporation of bortezomib into conditioning with melphalan [26], propylene glycol-free melphalan [27,28] and pharmacokinetically-directed melphalan dosing which has the potential to more precisely individualise therapy since body surface area-based dosing of melphalan is associated with significant inter-patient variability in melphalan exposure.

In the context of novel regimens that rapidly induce deep haematologic remissions the role of high dose therapy and SCT in AL amyloidosis will necessarily evolve. Patients with advanced organ disease who achieve optimal haematologic response to induction therapy are unlikely to benefit from high dose melphalan in the frontline setting. Rather, these patients who are at greatest risk of toxicity from SCT may become better candidates once their organs have time to improve.

Recommendation: Full high dose melphalan at 200 mg/m^2 is the preferred conditioning regimen prior to SCT and

modified dose melphalan at 140 mg/m^2 should be used for patients with reduced renal function.

Consolidation and maintenance therapy following SCT

High dose melphalan and SCT can induce remissions in patients with AL amyloidosis, in approximately 40%–50% of patients achieving haematologic CR. As a concept, consolidation therapy is commonly defined as a distinct course of therapy, usually same regimen as induction therapy, consisting of a limited number of cycles with the aim to increase the depth of the haematologic response and, subsequently frequency of organ response and overall outcome. Maintenance therapy, on the other hand is intended to be applied for a prolonged amount of time with the goal of preventing haematologic progression and subsequent organ deterioration.

Few data exist to guide management in these settings.

- Phase II data suggest bortezomib and dexamethasone (BD) administered to patients with AL amyloidosis who had not achieved CR at 3 months post-SCT was associated with an 86% improvement in haematologic response and all patients responded within 1 cycle [29].
- A retrospective study by the Mayo clinic group evaluated 471 patients with AL amyloidosis who underwent SCT and identified 72 (15%) who received consolidation with proteasome inhibitors (PIs) (33%), immunomodulatory agents (IMiD) (29%) or PIs and IMiDs (28%). The CR rate improved from 11% to 40% with consolidation. Patients with <VGPR who received consolidation had better PFS (median 22.4 versus 8.8 months, $P<.001$) and a trend towards better OS. In patients with ≥ VGPR post-SCT, consolidation did not improve PFS or OS [30].
- A single retrospective study analysed 50 patients with AL amyloidosis who underwent SCT including 28 patients who received maintenance therapy for longer than 6 months post-transplant, most with IMiD-based maintenance, primarily lenalidomide. No significant difference in PFS ($P=.66$) or OS ($P=.32$) was demonstrated including among patients with a high burden of bone marrow plasma cells (BMPCs) (> 10%) at baseline [31].
- A clinical trial using Ixazomib as maintenance post-ASCT in patients with AL amyloidosis who have >10% BMPCs at diagnosis is currently accruing (ClinicalTrials.gov identifier: NCT03618537).

Taken together, the available data suggests a potential role for a limited course of consolidation in patients with < VGPR post-SCT with the goal of inducing deeper remission. Consolidation therapy may certainly have a role in those who achieved a < VGPR post-SCT and did not receive induction therapy prior to SCT. However, the potential benefit of consolidation must be balanced with the risk of toxicity. For patients who achieve ≥ VGPR after SCT but have ongoing organ impairment or organ deterioration, it must be recognised that deeper haematologic response may not confer organ response or improvement. Maintenance after high dose therapy and SCT has not been routinely used or systematically studied in AL amyloidosis and there does not appear to be a role for long term lenalidomide-based maintenance therapy. Lenalidomide-based dose adjusted maintenance therapy can be instituted post-SCT for those with multiple myeloma defining biomarkers (e.g. plasmacytosis >60% and/or serum free light chain ratio of >100) and multiple myeloma associated CRAB findings of hypercalcemia, renal failure, anaemia and lytic bone lesions. Ongoing studies will hopefully provide insight into the use ixazomib and daratumumab in this setting.

Recommendation: Consolidation and maintenance therapy not routinely recommended after SCT in AL amyloidosis.

Haematologic and organ responses

Deep and durable haematologic responses can be achieved after SCT in AL amyloidosis. Haematologic response assessment should be performed at 3–6 months after SCT, preferably at 3 months. Bone marrow aspiration and biopsy are not needed to assess for validated haematologic response but are required for assessment of minimal residual disease. Deep haematologic responses indicated by normalisation of serum free light chain levels along with absence of monoclonal protein in serum and urine by immunofixation electrophoresis are desirable [32]. The goal should be to achieve a complete haematologic response or very good partial haematologic response with an organ response. It is imperative to note that the organ responses can lag behind the haematologic response by 6–12 months and can continue to occur gradually over many years after SCT. Haematologic and organ responses predict for overall survival in AL amyloidosis. Institution of additional therapy directed towards the plasma cell dyscrasia should weigh the risks and benefits and follow complete recovery from the toxicities of SCT. It should not be instituted solely for organ progression in the setting of adequate haematologic response (≥VGPR), unless indicated by other measures and individualised.

Haematologic responses of partial response or better following SCT can be achieved in 80%–85% of patients; and haematologic complete response in 30%–50% of patients. Haematologic relapse occurs in 32% of patients after achievement of a CR at a median of 4.3 years (range, 1.4–21.5) [33].

Overall organ responses can be achieved in 54% of patients with renal involvement, in 62% of patients with cardiac involvement and in 56% of patients with liver involvement. Majority of patients achieving renal and cardiac responses achieved response at 6 or 12 months following SCT; ∼ 80% within 12 months post SCT. Impact of organ response on survival for each haematologic response category is also evident after SCT. Achievement of organ response for any given haematologic response has an overall survival benefit. Patients achieving haematologic VGPR with no organ response have lower overall survival [34].

Special circumstances

Patients with advanced single organ dysfunction due to AL amyloidosis have a potential to receive solid organ transplantation(s) or, in case of renal failure, be on renal replacement therapy and, can become suitable candidates for consideration of SCT. Data on outcomes of SCT in these groups remain limited. In renal patients, SCT can be undertaken before or after renal transplantation [35,36] whilst in cardiac (and the rare liver) transplant recipients, SCT is performed always after the organ transplantation [37]. The considerations in this special group includes fitness for SCT based on criteria for AL amyloidosis after the organ transplant, management of immunosuppression during stem cell harvesting and the impact of function of the transplanted organ on risks of SCT as well as the potential risk of (ir)reversible transplanted organ dysfunction during SCT.

Mycophenolate mofetil and azathioprine can interfere with stem cell mobilisation; the impact of calcineurin inhibitors is less pronounced but data remains limited. Withdrawal or modification of immunosuppressive drugs prior to stem cell mobilisation should be coordinated with the respective solid organ transplant teams to monitor for increase in risk of organ rejection.

Patients on dialysis can safely undergo SCT with TRM and morbidity comparable to patients with AL amyloidosis who are not on dialysis. In a series of 32 patients from Boston undergoing SCT on dialysis, the TRM was 8% with a complete haematologic response achieved in 70% and median overall survival 5.8 years (8 years for patients in CR) [10]. A study at the Mayo clinic of patients with advanced renal amyloidosis showed that whilst requirement for dialysis during or soon after SCT was associated poorer outcomes, being on dialysis at the time of SCT did not have an adverse impact on prognosis. Experience of a small number of patients with AL amyloidosis undergoing SCT following renal transplantation suggests no adverse impact of renal graft function or loss of renal graft due to complications during SCT and longer term patient outcomes determined by depth of haematologic response.

Highly selected younger patients with advanced end stage cardiac AL amyloidosis may be suitable for heart transplantation (HT) as a lifesaving procedure. The need for deep and prolonged suppression of the amyloidogenic light chains following heart transplantation to prevent amyloid recurrence makes highly effective anti-plasma cell treatment an important component of the pathway. The UK group initially reported series of five patients undergoing successful SCT following a heart transplant. Recently, a US collaborative group reported nine patients who underwent SCT at median 13.5 months following HT with median OS of 87.5% at 1 year and 76.6% at 5 years. The experience from Boston of 8 patients undergoing sequential HT-SCT suggests outcomes were comparable to institutional results for non-amyloid HT recipients' (OS of 60% in amyloid vs. 64% in nonamyloid HT at 7 yrs. (p=.83)). Limited data on patient outcomes as well as the additional risks and interaction of chemotherapy with immunosuppression as well as potential cardiac toxicity or higher risk of organ rejection (with IMiD's) are important considerations in decisions about the choice of anti-plasma cell therapy following heart transplantation [38]. All patients undergoing consideration for a heart transplant should also be assessed by an experienced transplant team for eligibility for SCT: the suitability for sequential HT-SCT should be a consideration in selection of suitable candidates for a heart transplant.

Patients with advanced liver amyloidosis often have significant involvement of other organs and are rarely organ transplant candidates: although, should a patient receive a successful liver transplant for end stage liver amyloidosis, SCT as a consolidation/treatment procedure can be considered if the patient satisfies the other standard inclusion criteria.

Supportive care

Supportive treatment aimed at preventing and minimising complications during pre, peri and post-SCT period has an important impact on survival. Supportive care should be considered a fundamental part of an integrated treatment approach to these patients and requires the coordinated expertise of several specialists who are familiar with this disease.

Stem cell mobilisation and collection phase

- Stem cell mobilisation should be performed preferably with GCSF +/− plerixafor.
- Patients with significant cardiac involvement and CHF should undergo stem cell mobilisation with GCSF and planned plerixafor to avoid excessive fluid retention.
- Patients should be assessed daily (before and after stem cell collection) during this phase and volume overload should be managed with intravenous loop diuretics.
- Use of cardiac monitoring/telemetry is recommended in patients with cardiac involvement and CHF, hypotension, presyncope or arrhythmia.
- Hypotension from autonomic neuropathy should be managed with midodrine, compression stockings, prevention of intravascular volume depletion and droxidopa.

Peri-stem cell transplantation phase

- G-CSF post SCT should be given till neutrophil engraftment
- Antimicrobial prophylaxis – fluoroquinolone, acyclovir or valcyclovir, fluconazole, if allergic to fluoroquinolone, consider penicillin or doxycycline in consultation with infectious disease based on antibiogram for the institution
- GI prophylaxis with proton pump inhibitor
- Transfusion parameters, Haemoglobin of <8 g/dL for blood transfusion, Platelet count of <10 k or <20 k if bleeding and with fever for platelet transfusion, Platelet count of <50 k if factor X level 25%–50%, spleen and/or liver involvement, GI bleeding or severe mucositis for platelet transfusion
- Febrile neutropenia: follow institutional guidelines, avoid aminoglycosides for the risk of nephrotoxicity

- Special circumstances: Albumin infusion if serum albumin <2 g/dL due to advanced nephrotic syndrome, can be repeated daily or few times a week; cardiac monitoring with telemetry for all patients with cardiac involvement; avoidance of beta blockers and calcium channel blockers if atrial fibrillation occurs; consideration for amiodarone prophylaxis in patients with cardiac arrhythmias or Holter monitor with ventricular ectopy; judicious use of midodrine for blood pressure support; loperamide and diphenoxylate/atropine (Lomotil) use for melphalan-induced diarrhoea
- Engraftment syndrome (ES) - Engraftment syndrome encompasses a continuum of peri-engraftment complications after SCT. ES may include non-infectious fever; skin rash; diarrhoea; hepatic dysfunction; renal dysfunction; transient encephalopathy; and capillary leak features, such as non-cardiogenic pulmonary infiltrates, hypoxia and weight gain with no alternative etiologic basis other than engraftment. The incidence of ES has been reported to be 7%–48% after SCT in AL amyloidosis [39]. Management of ES should focus on exclusion of other aetiologies of the syndrome and supportive care and steroids if symptoms persist after 48–72 hours. It is important to note that steroids can worsen volume overload in patients with cardiac and renal involvement from AL amyloidosis.

Post-stem cell transplantation phase

- Antimicrobial prophylaxis for VZV to be continued for 12 months post SCT
- Prophylaxis for pneumocystis pneumonia to be continued for 3 months post SCT
- Immunisation schedule per institution policy

Role of transplant centre

Early mortality related to complications of SCT is worse in centres that perform fewer than four per year SCTs for AL amyloidosis. Early mortality rates of 5% at 30 days and 7% at 100 days compared with 1% at 30 days and 3% at 100 days for centres that perform greater than four per year SCTs for AL amyloidosis. Benefit of high volume centres was demonstrated in a large CIBMTR research study [40].

Limitations

These guidelines are represented as opinions of the key and experienced leaders in the field of SCT in AL amyloidosis since there are not many randomised clinical trials or evidence based data on this topic of this rare disease.

Conclusion

High dose chemotherapy and stem cell transplantation can lead to high haematologic and organ responses and prolonged survival in patients with AL amyloidosis, however, careful patient selection, melphalan conditioning regimen, appropriate supportive care and experience of the treatment centre are crucial to the success. With the efficacy and tolerability of many non-SCT treatment regimens, we must continue to build on this improvement and incorporate time-tested strategy of SCT in combination with these agents to further improve the outcomes in AL amyloidosis.

Disclaimer

These recommendations are meant to assist clinicians in making decisions regarding treatment of patients with amyloidosis. Adherence to these recommendations will not ensure successful treatment in every situation. Furthermore, these recommendations should not be interpreted as setting a standard of care, or be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgement regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biological behaviour of the disease. These recommendations reflect the best available data at the time this document was prepared. The results of future studies may require revisions to the recommendations in this document to reflect new data.

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