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Recent guidelines for high-dose chemotherapy and autologous stem cell transplant for systemic AL amyloidosis: a practitioner's perspective

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ABSTRACT

Introduction: High-dose melphalan followed by autologous stem cell transplant (ASCT) has been transformative in treating AL amyloidosis since the early nineties. Recently, the European Hematology Association (EHA) and International Society of Amyloidosis (ISA) have developed a combined guideline for the management of patients undergoing an ASCT for AL amyloidosis.

Areas covered: In this practitioner's perspective, we review the guideline, focusing on 6 major areas and offer practical advice for its application. We provide a perspective on the optimal use of ASCT and its potential application in the future.

Expert opinion: The EHA-ISA guideline comprehensively outlines the practicalities of performing an ASCT in AL amyloidosis. The critical aspect is careful patient selection. Vigilant fluid balance assessments are crucial as associated complications are common and dangerous. The role of ASCT is changing with improving hematological responses associated with novel agents. Evidence is limited for the use of ASCT in patients who achieve a complete hematological response (CR). Therefore, ASCT should be considered for those who only achieve a very good partial response (VGPR)/partial response (PR) and fulfil the strict selection criteria. Future research identifying the cohort who would benefit most from ASCT in the era of novel therapies is warranted.

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1. Introduction

Light-chain (AL) amyloidosis is a systemic disease associated with a plasma cell dyscrasia or B-cell lymphoproliferative disorder characterized by the misfolding, aggregation and deposition of free light chains resulting in progressive organ dysfunction [1]. Current treatment strategies focus on eliminating the underlying clonal disorder thereby reducing the production of the amyloidogenic light chain allowing for slow natural macrophage-led amyloid removal from affected organs [2].

High-dose intravenous melphalan followed by autologous stem cell transplantation (ASCT) was transformative in the treatment of patients with AL amyloidosis when originally reported in the early nineties [3]. Whilst an initial phase III trial failed to demonstrate benefit for ASCT [4] more recently, a head-to-head comparison of Melphalan plus Dexamethasone vs. ASCT favored ASCT with better median progression-free survival (PFS) (1.63 years vs. 4 years), median overall survival (OS) (6.53 years vs. not achieved) and 12-month complete hematological remission (CR) (Overall Risk (OR) 4.84) [5]. When first used, treatment-related mortality (TRM) was nearly 15–18.8% but in the contemporary cohorts has reduced to 1.1–2.5% with improving response rates and increasing overall survival [6,7]. The improvement in TRM is largely due to better patient selection and improvements in peri-transplant management.

With advances in therapeutics such as Bortezomib [8,9], Daratumumab [10], or other monoclonal antibodies that demonstrate clinical efficacy in AL amyloidosis alongside the emergence of novel therapies such as CAR-T therapy in multiple myeloma [11,12], the role of ASCT in AL amyloidosis is debated. In a retrospective study comparing Bortezomib vs ASCT, Sharpley et al. demonstrated no clear survival advantage in those receiving ASCT compared to those receiving Bortezomib alone [13] although there was still an improved time to next treatment (TTNT).

The key advantages of ASCT include a one-off treatment that is cheaper than Daratumumab-based regimes (an important consideration in cost constrained treatment scenarios) and a prolonged PFS for patients achieving a complete remission. This has shifted the questions about the role of ASCT in AL amyloidosis from one of eligibility and fitness to one of appropriateness with respect to treatment goals. With more patients achieving a CR following induction therapy there are questions surrounding the impact and timing of ASCT following such efficacious treatment [14]. This was highlighted by the ANDROMEDA trial which compared Daratumumab plus VCD (bortezomib cyclophosphamide dexamethasone) vs. VCD alone and resulted in an overall response rate (ORR) of 92% vs. 77% and CR rate of 42% vs. 13% for the Daratumumab plus VCD arm. The higher rates of a complete hematological

Article highlights

- There is a clear role for high dose melphalan followed by autologous stem cell transplant in patients with AL amyloidosis outlined by the newly published EHA-ISA guidelines
- Careful patient selection is critical to the success of an ASCT in AL amyloidosis
- In our opinion, the majority of patients should receive a Bortezomib based induction therapy irrespective of bone marrow plasma cell percentage
- Personalised supportive care and regular fluid status assessment throughout the transplant period, including the stem cell mobilisation and collection phase, is critical
- The optimum use of ASCT in an era of Daratumumab and novel therapies is an area requiring further research and clinical trials; we propose ASCT should be reserved for those not achieving a CR after induction
- Deferred ASCT should be considered for a cohort of patients initially ineligible but improve eligibility following induction

response using a quadruplet therapy will impact the use of ASCT and place it in a more nuanced role, potentially for those who are MRD (minimal residual disease) positive or who only achieve a very good partial response (VGPR) after induction therapy [15].

Despite these questions, ASCT currently remains one of the most important standard treatments for the management of AL amyloidosis. Approximately, 15–20% patients are eligible at diagnosis for ASCT and a further small proportion of patients may become eligible following first-line therapy [16]. Publication of the guidelines by European society of hematology (EHA) – international society of amyloidosis (ISA) working group has been a milestone that may help to standardize ASCT in AL amyloidosis [17].

In this ‘Practitioners Perspective,’ we focus on these guidelines and speculate on the future of ASCT in AL amyloidosis. We highlight the need for careful patient selection, the role of induction therapy, the consideration of maintenance or consolidative chemotherapy following transplantation and supportive care in ASCT.

2. Patient selection

Patient selection has proved critical in reducing TRM in AL amyloidosis [18,19]. The current selection criteria (Table 1) recommended by the EHA-ISA group are broad and comprehensive. They include the overall performance score, assessment of specific organ function and highlight definitive exclusion criteria. These are now considered as a standard of care and should be strictly followed.

The use of dose-reduced Melphalan (140 mg/m²) is only recommended in the context of those with reduced renal function (eGFR <30 mL/min/m²), and not due to patient factors. A patient not fit for full-dose Melphalan, for reasons aside from renal dysfunction, should not be considered a transplant candidate due to the significant reduction in complete response rates and availability of highly effective alternative therapies. ASCT should be delayed in patients approaching dialysis and ideally dialysis should be established prior, with view to a deferred ASCT [20,21].

An important factor for patient selection is the extent of proteinuria and hypoalbuminemia (both not specifically covered in the guideline). Renal involvement is apparent in 60% [9] to 80% [22] of patients with AL amyloidosis although the quantity of the proteinuria per se does not impact outcomes. We reported that patients with nephrotic range proteinuria have a higher TRM than those with lower proteinuria [23] but those patients with nephrotic syndrome (>3 g/day) who respond will also benefit from ASCT [22,24].

Patients with a low serum albumin (<20 g/L) have an increased risk of complications particularly during stem cell mobilization and are at a higher risk of acute kidney injury during the ASCT [22,25]. Low serum albumin is a greater risk factor than absolute degree of proteinuria when considering ASCT [26]. Careful consideration is needed when undertaking ASCT for patients with serum albumin <20 g/l due to the higher risk of AKI. .

Patients with extensive gastrointestinal involvement or Factor X deficiency are at risk of serious and life-threatening bleeding during high-dose melphalan conditioned ASCT and, whilst not necessarily a contraindication, should be an important factor into their suitability for ASCT. Significant hepatic involvement is often associated with these risk factors and patients with extensive hepatic amyloidosis need careful screening.

3. Induction therapy

The recommendation from the EHA-ISA working guideline is that induction therapy with a Bortezomib-based regime ± Daratumumab for 2–4 cycles should be considered if bone marrow plasmacytosis is greater than 10%. The key point in the guideline is that ASCT should be undertaken in all suitable patients who achieve less than a CR. The guideline also suggests that transplantation be deferred if a hematologic CR is achieved with induction therapy.

Since the median bone marrow plasma cell infiltration at diagnosis is ~11%, nearly half of newly diagnosed patients will present with bone marrow infiltration of <10% [27,28] – a group not recommended for induction treatment in the EHA-ISA guidelines. In the only randomized phase III control trial of Bortezomib + Dexamethasone plus ASCT vs. ASCT [29] the median plasma cell infiltration of both groups was 3.2 ± 2.7% and 2.8 ± 2.1% respectively. The study demonstrated an improved OS and PFS in the group who received Bortezomib and Dexamethasone induction. The retrospective analysis from Center of International Blood and Marrow Transplant Research (CIBMTR) showed both survival and response benefit for all patients receiving induction chemotherapy in AL amyloidosis prior to ASCT [30].

We would recommend that all patients, irrespective of the bone marrow plasma cell infiltration, receive appropriate PI-based induction. The option of incorporating Daratumumab as part of a standard induction template must be considered carefully, given a early suggestion of higher TRM noted in patients on the ANDROMEDA trial treated with daratumumab undergoing ASCT – the numbers are small and this data needs confirmation [31]. A very select subgroup of patients with isolated neuropathic amyloidosis (where bortezomib-based treatment is not possible) or rarely, patients with an IgM AL

Table 1. Selection criteria from the EHA-ISA guideline [17] with additions from a practitioner's perspective (revisions in red).

<p>Definite exclusions for SCT in AL amyloidosis are as follows:</p> <ul style="list-style-type: none"> •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 or/and evidence of active bleeding •Extensive GI involvement with evidence of active GI bleeding or risk of bleeding
<p>Broad eligibility criteria for SCT in AL amyloidosis are as follows:</p> <ul style="list-style-type: none"> •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 $\geq 40\%$, 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/m² (Patients with eGFR <30 mL/min/m² and not yet on dialysis are at an increased risk of worsening of renal function during SCT) •Patients on chronic and stable schedule of dialysis for ESRD should not be excluded if other eligibility criteria met
<p>Practitioner's additional desirable criteria for SCT</p> <ul style="list-style-type: none"> •Serum albumin of >20g/l •Lack extensive hepatic amyloidosis •eGFR >30 ml/min

amyloidosis could be considered for upfront high-dose melphalan conditioned ASCT without induction chemotherapy.

We would consider ASCT for all eligible patients who achieve less than a CR following induction chemotherapy. The role of ASCT for patients achieving a CR following induction treatment remains unclear. It is known that patients who achieve a CR or difference between involved and uninvolved free light chains (dFLC) <10 mg/l or involved free light chain (iFLC) < 20 mg/l following induction therapy have the most superior overall survival following first-line therapy [32]. Evidence is lacking on the impact of ASCT in this specific cohort of patients and there is a real risk of TRM. For patients achieving a CR, especially those who have a low plasma cell

burden at diagnosis (i.e. <10%) more evidence is required to assess the benefit of ASCT following induction.

The guidelines also do not recommend ASCT for patients with bone marrow plasma cell burden >10% and a CR following induction – this point remains contentious especially in cost constrained environments where access to multiple novel agent-based therapies may not be possible and data on outcomes for transplanting such patients in relapse remains scant.

The precise role of MRD in AL amyloidosis informing treatment choice is not yet well studied. Since the goal of therapy in AL is organ response, consideration of an ASCT could be given to those with persistent MRD with a clear lack of organ

response post induction [33]. Given the delayed nature of organ response in AL amyloidosis, a deferred ASCT could be a reasonable option in this situation but remains an area of active research.

We reported the benefit of ASCT in a small series of patients who were initially transplant ineligible but then had an organ response following induction therapy and became eligible for ASCT [16]. We consider a deferred consolidative ASCT when patients achieve eligibility and hence, in all potentially transplant eligible patients, a stem cell sparing first-line regime is important.

From a practitioner's perspective all cases require multidisciplinary review and decisions made on a case-by-case basis using the suggestions above in context of the published guidelines: patients with >10% plasma cell burden, younger patients without significant organ damage, patients in CR with lack of organ response and persistent MRD are all candidates for a consolidative ASCT. It is our opinion that ASCT *per se* is probably not appropriate in patients in a complete response with low starting clonal burden unless there is clear evidence of clonal persistence and lack of organ response. In contrast, any patient on the cusp of eligibility who achieve a CR or VGPR with organ response should remain under active surveillance.

4. Stem cell mobilization and collection

Stem cell mobilization and collection in AL amyloidosis has been associated with significant mortality [26]. The EHA-ISA guideline highlights the risks of hypotension, hypoxia, cardiac arrhythmias and fluid retention. Patients with congestive heart failure or nephrotic syndrome are at particular risk. The recommendation from the EHA-ISA guideline is to use 10–16mcg/kg/day of G-CSF (single or split dose) for 3–4 days prior to mobilization in conjunction with Plerixafor for those with cardiac involvement. The recommended target dose of CD34+ cells is $4\text{--}5 \times 10^6$ CD34+ cells/kg (minimum 2.5×10^6 cells/kg). Due to the risk of significant toxicity [34], chemotherapy-based mobilization regimes (with cyclophosphamide alone or in combination) are not recommended except in highly selected cases with failure to mobilize otherwise.

The need for regular monitoring of fluid balance during mobilization is critical. Patients with high N-terminal pro-brain natriuretic peptide (NT-ProBNP), a low serum albumin or raised intraventricular septal thickness are at a higher risk of complications during mobilization and collection and should be scrupulously monitored [35]. We would advise daily weight monitoring and a plan to intervene early especially if there is 2 kg weight gain. We advise the use of loop diuretics in the first instance if fluid retention becomes apparent.

We also strongly advise against the use of Cyclophosphamide as part of stem cell mobilization due to the cardiac and other organ side effects. The guideline highlights these risks and is in keeping with our practice to mobilize with G-CSF ± Plerixafor.

The need for 'rain' day stem cell collection in all patients potentially eligible for transplant but not necessarily proceeding to transplantation remains has to be based on local

resources including long term stem cell storage facility/costs. Any eligible patient treated with a potentially stem cell damaging agent in the induction regime (e.g. an immunomodulatory agent) should undergo collection after completing 4 cycles of treatment (as per the protocols used for multiple myeloma) [36]. Ideally, sufficient stem cells should be collected for 2 ASCTs but patients should not be re-mobilized if the initial collection is inadequate.

5. Conditioning

The preferred conditioning regime recommended in the guideline is Melphalan 200 mg/m². There is some suggestion that splitting the dose over 2 days may reduce toxicity and this has been standard practice in our center based on the protocol developed at Boston University Medical Center [37]. Patients with IgM-related AL amyloidosis with an underlying lymphoproliferative disorder may gain additional advantage with the use of BEAM (BCNU, Etoposide, Cytarabine, Melphalan) as conditioning but data is limited and this should be reserved for very fit patients [38].

The guideline also comments on the use of modified-dose melphalan (140 mg/m²) in patients with reduced renal function. There is evidence that modified-dose Melphalan can result in good hematological response rates and prolonged survival especially when a CR is achieved [39]. This regime should be limited to patients only with an eGFR of <30 ml/min/m².

Our personal approach is to avoid ASCT in patients with an eGFR of <30 ml/min/m² and delay ASCT until patients are established on dialysis or following organ response post induction therapy. Alternatively, delaying ASCT until first relapse is a reasonable option in this situation.

6. Consolidation

The guideline does not recommend routine use of maintenance therapy following ASCT. There is a clear caveat for patients who fulfil criteria for multiple myeloma in which maintenance as per institutional standard for multiple myeloma should be considered [40].

Data from the Sloan Kettering group has shown that post-transplant bortezomib may achieve deep and durable complete responses [41]. In our opinion, patients who do not achieve at least a VGPR following ASCT should be considered for a further regime as second line using at least one agent that was not part of the induction regimes especially if there is cardiac amyloidosis present.

7. Supportive care

When compared to ASCT in multiple myeloma whose TRM is 1.6%, the TRM in AL amyloidosis is higher [42]. As stated, this is due to the unique nature of the condition particularly with respect to the cardiac and renal complications. Supportive care around ASCT in AL amyloidosis should be focused on mitigating this risk. Major complications include pulmonary edema, cardiac arrhythmias, fluid retention, acute renal failure, hypotension and engraftment syndrome which risk triggering

Table 2. Supportive care in the stem cell mobilization and collection phase, the peri-transplant phase and post-transplant phase as per the EHA-ISA guidelines with practitioner's additions in italics.

Stem cell mobilisation and collection phase
<ul style="list-style-type: none"> • Stem cell mobilisation should be performed preferably with G-CSF +/- plerixafor. • Patients with significant cardiac involvement and CHF should undergo stem cell mobilisation with G-CSF 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. • <i>Avoid using cyclophosphamide in stem cell mobilisation</i>
Peri-stem cell transplantation phase
<ul style="list-style-type: none"> • G-CSF post SCT should be given till neutrophil engraftment • Antimicrobial prophylaxis <i>from day +2-3 and continue until neutrophil engraftment.</i> • GI prophylaxis with proton pump inhibitor • Transfusion parameters to maintain: Haemoglobin of >80g/L (>100g/L for cardiac patients), Platelet count of >20x10⁹/L, for those at higher risk of bleeding platelet count of >30x10⁹/L • Febrile neutropenia: follow institutional guidelines • Consider albumin infusion if serum albumin <20 g/L due to advanced nephrotic syndrome • 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 significant ventricular ectopy • Judicious use of midodrine for blood pressure support • Loperamide and diphenoxylate/atropine (Lomotil) use for melphalan-induced diarrhoea • 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
<ul style="list-style-type: none"> • Antimicrobial prophylaxis for VZV, pneumocystis as per institutional standard • Post transplant COVID primary re-immunisation from 3 months • Other Immunisation schedule per institution policy

progressive organ failure. The risks with stem cell mobilization are already detailed above.

The critical factor during ASCT for AL amyloidosis is fluid management. Patients with cardiac involvement remain at risk of developing pulmonary edema especially with rapid fluid resuscitation for hypotension or excessive fluid replacement. Conversely, patients with renal amyloidosis are at high risk of acute kidney injury due to pre-renal factors if fluid replacement is not adequate. Hence, meticulous fluid replacement is critical to the success of ASCT and to avoid end organ dysfunction. Twice daily weight assessment and the maintenance of adequate blood pressure with measured fluid replacement

is important. In hypotensive patients (sepsis or hypovolaemia), careful fluid boluses of 250 ml 0.9% saline should be administered with regular blood pressure monitoring.

From a clinician's perspective, the guideline sets out clear advice (Table 2) for supportive therapy in the stem cell mobilization and collection phase, peri – stem cell transplantation phase and post – transplant phase.

Whilst there is no published data, use of prophylactic broad-spectrum antibiotics as per institutional standards and resistance patterns during the period of neutropenia is strongly recommended. This may avoid the sepsis-related 'hypotensive hit,' which can trigger multiorgan failure. In our

practice, we start antimicrobial prophylaxis from day +2-3 and continue until neutrophil engraftment.

Close discussion with intensive care physicians early on in the transplant period is suggested in order to facilitate the use of vasopressor support if required.

For patients with cardiac and renal involvement, as per the guideline, we advise the administration of 20% Human Albumin Solution (HAS) on a daily (or twice daily if <20 g/l) to manage fluid retention. The main goal is to allow better fluid management rather than achieve a target albumin. Based on the personal experience of the authors in a small patient cohort there may be a role for 20% HAS replacement in patients with low albumin prior to conditioning as melphalan is highly albumin bound and low serum albumin may potentiate melphalan toxicity, particularly with respect to the development of an AKI [23,25,43].

Arrhythmias are a significant concern in cardiac patients in the peri-transplant period especially atrial fibrillation. Patients with cardiac AL amyloidosis may develop bradycardia if the stem cell re-infusion is given too quickly probably due to the dimethyl sulfoxide (DMSO). There may be a role for prophylactic anti-arrhythmic treatment with amiodarone in higher risk patients.

Patients with AL amyloidosis can have hemostatic impairment [44]. This can be a bleeding propensity via multiple mechanisms including hemostatic deficiencies such as Factor X deficiency or due to amyloid deposition, particularly in the gastrointestinal tract. The guideline has a platelet transfusion threshold for those at risk of bleeding and our practice is to maintain platelet counts $>30 \times 10^9/L$ for such patients.

In contrast, patients with nephrotic syndrome (serum albumin of <25 g/l) or those in atrial fibrillation with CHADS2-VASC2 score of 2 or higher should be anticoagulated. In our practice, in the peri-transplant period, we advise the use of low molecular weight heparin with a tapering dose, stopping during period of severe thrombocytopenia and restarting aligned to the platelet count.

8. Conclusion

The recently published EHA-ISA guideline provides a comprehensive overview for the use of ASCT in AL amyloidosis. It highlights the need for careful patient selection and the specific complications that may arise in the peri-transplant period. However, there is a paucity of data surrounding the role of ASCT in the context of a low plasma cell burden or its role in consolidating those who achieve a complete hematological response following induction therapy.

9. Expert opinion

In this perspective piece, we have examined the EHA-ISA guideline focusing on the practicalities of performing an ASCT in AL amyloidosis. We agree with the guideline that all ASCTs for AL amyloidosis should be undertaken in a center that has experience with AL amyloidosis transplants (suggestion is a minimum of 4 AL transplants annually [19]).

The role of ASCT in AL amyloidosis is changing. The goal of therapy is to eliminate, as best and as rapidly as possible, the

underlying plasma cell clone thereby restricting the production of the amyloidogenic light chain. ASCT has stood the test of time in achieving deep and durable responses translating into improved survival and gain in quality of life. However, with novel agent-based induction treatment such as daratumumab containing regimes, very high deep response rates are achieved prior to ASCT. The role of ASCT in these responders has now become less clear, at least in the first remission [45,46].

Contrastingly, a recent study demonstrated very few complete responses following ASCT undertaken when patients were refractory to induction treatment, therefore ASCT in this setting is questionable [47]. It is reasonable to undertake second-line treatment prior to transplantation in such cases.

Further research is required to determine the optimal timing of ASCT and optimal cohort of patients. Strict selection criteria limit the use of ASCT but establishing which patients will benefit the most from ASCT is still to be determined, especially in the age of Daratumumab given its high complete response rate. With anti-fibril therapies such as CAEL 101 or GSK2315698 which are currently in the trial phase, the role of conventional chemotherapy including ASCT may be further condensed [48–50]. If these are positive, ASCT may have to undergo a further re-appraisal as many more patients with improved organ function will become potentially transplant eligible.

The benefits of ASCT are clearly established in AL amyloidosis, especially for patients achieving a CR post-ASCT [5,51]. There is evidence to suggest patients who have undergone ASCT as part of first-line therapy are also more likely to achieve MRD negativity. In a series of 25 patients, those who received an ASCT had a higher rate of MRD negativity 3 months following therapy versus those who received induction therapy alone (90.0% vs 53.3%, $p = 0.043$) [52]. However, in a larger cohort there was no difference in MRD positivity rates in patients who underwent an ASCT (MRD negative 52% vs. MRD positive 47% $p = 0.8$) although direct comparisons between treatments (ASCT vs. No ASCT) could not be made [53].

A specific consideration where ASCT will maintain a crucial role is in a resource constrained setting where treatment for AL amyloidosis with agents like daratumumab are not accessible or affordable. ASCT is a highly cost-effective treatment with proven long-term benefit and will play a vital role in the management of AL amyloidosis.

Ultimately, the role of ASCT in the future will be determined by the requirement to achieve a deep response and subsequently by whether an alternative therapy is more efficacious, safer and more cost-effective. The assessment for depth of response in AL amyloidosis is currently based on urinary and serum light-chain quantification, however, this may change with the use of mass spectrometry to determine the presence of amyloidogenic light chains [54]. The benefit of ASCT in patients with or without MRD negativity has yet to be considered and is an area of necessary further research.

There remains a reasonable TRM with ASCT, in the region of 2% and specialist management is required in the peri-transplant period. Practically, the role of ASCT may also be

limited by patient preference to be treated locally which needs to be considered; an issue recognized when treating patients with multiple myeloma [55]. With therapies becoming available that require fewer inpatient days, fewer intravenous medications and better side effect profiles the role of ASCT will be limited by a new risk/benefit balance [56]. This, in turn, is likely to reduce the volume of transplants performed, thus limiting the experience of treating centers which will ultimately be detrimental to patient outcomes from ASCT.

ASCT remains the standard of care for eligible patients with AL amyloidosis. Better patient selection and peri-transplant management has radically improved treatment-related mortality but there remain complications specific to AL amyloidosis that require specialist input. The EHA–ISA guideline provides a framework to manage patients undergoing an ASCT. The lack of randomized controlled trials assessing the efficacy of ASCT, especially in the Daratumumab era, bring to the fore the debate surrounding the optimal use of ASCT. From a practitioner's perspective, ASCT has an important role in the management of AL amyloidosis, but to optimize outcomes it requires the provision of a highly specialized service familiar with ASCT in AL amyloidosis and its intricacies.

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