

## \* CHAPTER 27

# HSCT for primary amyloidosis in adults

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## 1. Introduction

Primary systemic amyloidosis (AL) is a misfolding protein disease which leads to the extracellular deposition of abnormal protein fibrils in various tissues, including kidney, heart, liver, gastrointestinal tract, and peripheral nervous system, causing organ dysfunction. Amyloid fibrils in AL are constituted by a insoluble monoclonal light chain (LC) which aggregates forming  $\beta$ -pleated sheets. Diagnosis of AL is based on the recognition of amyloid substance in an appropriate tissue (subcutaneous fat tissue, rectum, bone marrow, involved organ), revealed by the characteristic staining pattern with Congo red dye, and further identification of amyloid fibril composition. Adequate identification of fibril precursor protein, a monoclonal LC, allows differentiation from other types of amyloidoses (familial type, secondary amyloidosis, dialysis-associated, senile). In most patients a monoclonal gammopathy is detected in serum and/or urine. Since AL is a clonal plasma cell disorder responsible for the synthesis of amyloidogenic LC, therapeutic agents used for AL therapy are similar to those used against multiple myeloma. Despite the usual low tumour burden characteristic of this disorder, AL is a poor-prognosis disease, with only a modest response pattern to standard chemotherapy, which cannot prevent progression of tissue damage. In contrast, intensive therapy with high-dose melphalan with auto-HSCT produces a high proportion of responses, followed by significant amelioration of organ damage in most responding patients. Unfortunately, this procedure is associated with an exceedingly high toxicity, reflecting the underlying organ damage secondary to amyloid deposits (1).

## 2. Indications

Treatment with high-dose melphalan followed by peripheral blood stem cell rescue (auto-HSCT) should be considered in younger patients, up to 65–70 years, diagnosed with systemic AL, with no limiting organ damage, i.e., in the absence of uncompensated cardiac failure, severe renal failure or marked increase in bilirubin, and suitable for such an intensive procedure.

## 3. Stem cell mobilisation and collection, and conditioning regimen

Stem cell mobilisation and leukapheresis in patients with AL is associated with unusual morbidity and with some reports of fatal events, due to the impaired organ and cardiovascular reserve of these patients. Thus, a syndrome of hypoxia and hypotension has been described both during mobilisation with G-CSF and during the leukapheresis procedure itself, probably as a result of diverse causes such as a capillary leak syndrome triggered by G-CSF, platelet activation during SC collection, and the release of inflammatory cytokines. Therefore, use of reduced doses of G-

CSF (5–6 µg/kg ever 12 hours) and careful monitoring during the leukapheresis procedure is highly encouraged, with admission if necessary to an Intensive Care Unit, in order to avoid or correct immediately any sudden volume imbalance (hypovolemia or fluid overload) that may arise during the SC collection process. Conditioning regimens in AL are based on high-dose melphalan. The usual melphalan dose is 200 mg/m<sup>2</sup>, although a “risk-adapted” approach, with dose reduction to 140 mg/m<sup>2</sup>, has been proposed in higher risk patients in order to decrease transplant-related toxicity (2). Proposed criteria for defining high risk patients are age >60, increased creatinine level, performance status (PS) 2 or compensated cardiac failure. Reduced melphalan dose has been associated with a decreased response rate in some studies (2, 3), although this observation has not been confirmed in other studies (4).

#### 4. Results: toxicity, response, and long-term outcome

Auto-HSCT is associated with a remarkably high risk of morbidity and mortality in patients with AL, with a TRM ranging from 11 to 43% (Table 1). Cardiogenic shock, fatal arrhythmias, gastrointestinal bleeding, and infections are the most frequent complications involved in procedure-related deaths during this phase. Infrequent causes such as spontaneous splenic rupture or DMSO-triggered cardiac arrest have also been reported in this setting. Furthermore, renal insufficiency develops frequently after auto-HSCT, occurring in approximately 20% of patients.

As regards activity against AL, high-dose melphalan results in significant responses in 50–60% of cases, with complete responses in about one third of patients. CR is defined, in this setting, by a negative immunofixation and normal free

**Table 1: Summary of the outcome of patients with primary amyloidosis undergoing autotransplant according to largest series**

Source	No. of pts	Overall response rate (CR) %	TRM (%)	Overall survival (%)
Boston (US) (3)	205	NR (40)	13 (100-day)	60 (3-yr)
CIBMTR (multicenter) (11)	107	32 (16)	18 (30-day) 27 (1-yr)	66 (1-yr) 56 (3-yr)
UK (multicenter) (12)	92	64 (35)	23 (100-day)	50 (5-yr)
Mayo Clinic (7)	282	71 (33)	11 (100-day)	60 (5-yr)
French Intergroup (MAG-IFM) (9)	50	49 (30)	24 (100-day)	45 (3-yr)

CR: complete response; TRM: transplant-related mortality; NR: not reported; CIBMTR: Center for International Blood and Marrow Transplant Research; UK: United Kingdom; MAG-IFM: Myélome Autogreffe-Intergroupe Francophone du Myélome

immunoglobulin light-chain (FLC). Interestingly, haematologic responses are followed by organ responses, i.e. improvement of involved organ function, in most cases. Although median time to achieve a response is between 3–4 months, responses can take several months, up to 2 years, in some patients. On the other hand, some relapses are observed during follow-up, although the overall incidence of relapses is relatively low, especially among patients who achieve CR after auto-HSCT. Thus, the relapse incidence at 10-years among CR patients was 21% in the Boston series (3). These combined results translate into a long-term survival between 45–60%, according to larger series (Table 1).

Guidelines for an adequate evaluation of potential candidates to an autotransplant, recommended clinical care following transplant and basic criteria for assessment of response after auto-HSCT are summarised in Table 2.

### 5. Prognostic factors

Several factors have been related to transplant outcome in AL. Thus, cardiac involvement, as assessed by several methods (congestive heart failure, thickened intraventricular wall on ultrasonography), is invariably identified as an adverse prognostic factor. In this regard, measurement of cardiac troponins (cTnT, cTnI) and pro-brain natriuretic peptide (NT-proBNP) provides a refined surrogate marker of myocyte damage in AL and these cardiac biomarkers are strong predictors of survival after auto-HSCT, with a significant shortened life expectancy among patients with increased levels (5). Concurrent renal failure is also associated with shorter survival after transplant and, in general terms, auto-HSCT is contraindicated in patients with severe renal failure. Variables related to disease extent also predict outcome after transplant. Thus, involvement of more than two organs correlates with an unfavourable prognosis (6). More recently, baseline level of FLC has been identified as a prognostic factor in this setting, with an increased risk of TRM in patients with higher pre-transplant levels (7). Of note, the degree of response achieved after transplant showed a striking correlation with long-term outcome, with the most favourable outcome observed in patients who achieved CR (8). On the contrary, patients who fail to achieve a significant response show a poor outcome, with rapid disease progression.

### 6. Role of auto-HSCT in the management of the disease: comparison with other treatment approaches

Long-term survival after auto-HSCT appears to be prolonged, especially in patients who achieve CR after transplant, and compares favourably with historic controls. This observation, however, should be interpreted with caution as it might reflect

**Table 2: Specific considerations regarding evaluation of auto-HSCT in patient with primary amyloidosis**

<b>Diagnostic accuracy</b>	<ol style="list-style-type: none"> <li>1. Demonstration of amyloid deposition in an appropriate tissue (Congo Red staining)</li> <li>2. Confirmation of primary origin AL: <ul style="list-style-type: none"> <li>- Presence of monoclonal light chain in amyloid fibril</li> <li>- (or) Detection serum/urine monoclonal light-chain</li> </ul> </li> </ol>
<b>Is the patient a candidate to an autotransplant?</b>	<ol style="list-style-type: none"> <li>1. Age up to 65–70 years</li> <li>2. Adequate performance status (<math>\leq 2</math>)</li> <li>3. Absence of limiting organ damage: <ul style="list-style-type: none"> <li>- No compensated cardiac failure</li> <li>- Severe renal failure</li> <li>- Markedly increased bilirubin</li> </ul> </li> </ol>
<b>Assessment of risk factors</b>	<ol style="list-style-type: none"> <li>1. Assessment of cardiac involvement: <ul style="list-style-type: none"> <li>- Determination of cardiac biomarkers (cTnT, cTnI, NT-proBNP)</li> <li>- Echocardiogram (interventricular wall thickness)</li> </ul> </li> <li>2. Assessment of amyloid deposition: <ul style="list-style-type: none"> <li>- Number of involved organs (renal, cardiac, hepatic, gastrointestinal, peripheral &amp; autonomic neuropathy)</li> <li>- Serum FLC measurement</li> </ul> </li> </ol>
<b>Recommended care during procedure</b>	<ol style="list-style-type: none"> <li>1. Monitor stem cell mobilisation and collection. Consider admission to an Intensive Care Unit</li> <li>2. Adequate risk-adapted conditioning: <ul style="list-style-type: none"> <li>- Standard dose: melphalan 200 mg/m<sup>2</sup></li> <li>- Reduced dose (if concurring risk factors): melphalan 140 mg/m<sup>2</sup></li> </ul> </li> <li>3. Careful post-transplant management: <ul style="list-style-type: none"> <li>- Close monitoring of cardio-vascular function</li> <li>- Prevention of mucosal &amp; gastrointestinal bleeding: specific platelet transfusion policy (maintain <math>&gt; 50 \times 10^9/L</math>)</li> </ul> </li> </ol>
<b>Adequate assessment of post-transplant response</b>	<ol style="list-style-type: none"> <li>1. Haematologic response: <ul style="list-style-type: none"> <li>- CR: negative serum &amp; urine immunofixation; normal <math>\kappa/\lambda</math> ratio &amp; absolute value of FLC</li> <li>- PR: 50% reduction of serum M component, urine light chain &amp; FLC</li> </ul> </li> <li>2. Organ response. Re-assessment of specific parameters of pre-transplant involved organ: <ul style="list-style-type: none"> <li>- Renal (24-hour urinary protein, creatinine level)</li> <li>- Heart (functional class, septal thickness, ejection fraction)</li> <li>- Liver (alkaline phosphatase, liver size)</li> <li>- Nerve (nerve conduction)</li> </ul> </li> </ol>

merely a selection bias, since candidates for auto-HSCT constitute a selected population with better prognosis. Therefore, the precise impact of auto-HSCT in the management of the disease remains controversial; there are only a few studies

comparing auto-HSCT with standard dose chemotherapy and the results of these studies are conflicting. Thus, on the one hand, a case control-study conducted by the Mayo Clinic, which compared the outcome of 63 patients who had received an auto-HSCT with that of 63 patients treated with standard therapy, showed a better outcome in the intensively treated subgroup, with a 4-year survival of 71 vs. 41% (9). This study, despite matching for main variables, has some limitations derived from the retrospective nature of the study and therapy administered in the control group, which mostly consisted of melphalan and prednisone. In contrast, recently published results of the only randomised trial comparing high-dose melphalan with standard dose melphalan and dexamethasone showed a better outcome in patients not randomised to high-dose melphalan, when analysed on an intention-to-treat basis (10). This study, however, also has some limitations, such as the relatively small number of patients included, 50 *per arm*, and the low compliance with the assigned therapy, since only two-thirds of patients randomised to intensive therapy finally underwent auto-HSCT. When the analysis was restricted to patients who actually received the assigned therapeutic option, no major differences were observed between the arms. Therefore, the potential benefit of high-dose melphalan and the exact target population of AL patients remain to be clarified in further studies. Moreover, the potential improvement in the “control arm” (i.e., based on non-intensive therapy) with the introduction of newer agents such as immunomodulators (thalidomide, lenalidomide) or the proteasome inhibitor bortezomib, should be considered while assessing the therapeutic role of auto-HSCT in this disease.

## 7. Future perspective and conclusions

Given the relevance of achieving a response after transplant, several approaches for increasing the proportion of responses after auto-HSCT have been proposed. Thus, the Boston group is conducting a trial of tandem transplants, with performance of a second transplant with melphalan at a dose of 140 mg/m<sup>2</sup>, in patients not achieving CR after first transplant. The administration of post-transplant maintenance therapy with newer agents is another potential strategy for improving control of the disease. Finally, an allogeneic procedure using reduced-intensity conditioning has been performed in a minority of patients, with the aim of exploiting a possible “graft-versus-amyloidosis” effect.

In conclusion, auto-HSCT results in haematological responses and organ improvement in a significant proportion of patients with AL. Moreover, responding patients show a relatively prolonged survival. Nonetheless, this procedure is associated with a exceedingly high mortality, with a TRM of at least 10%, reflecting the fragile condition of patients due to multiorgan damage caused by amyloid deposition. Therefore, careful selection of patients for transplant is critical. In this regard, a

more refined assessment of cardiac involvement or the extent of the disease, by means of measurement of cardiac biomarkers and quantification of serum FLC, might contribute to a more accurate evaluation of patients prior to auto-HSCT. Nonetheless, the long-term effectiveness of high-dose melphalan for the management of the disease is currently unclear, and comparison with standard-dose agents shows conflicting results. Finally, development of new strategies to intensify and/or prolong response after auto-HSCT might improve the outcome. In this regard, further prospective studies are required to elucidate the role of auto-HSCT in AL.

## References

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## Mutiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/ebmt-handbook2008answers.htm>

1. **Regarding diagnosis of primary AL, indicate the correct answer:**
  - a) Diagnosis of AL relies exclusively on Congo Red positivity .....
  - b) A monoclonal light chain is rarely detected in serum .....
  - c) Congo Red staining must be performed in the involved organ .....
  - d) AL is generally a low burden monoclonal gammopathy, with a low level of plasma cell bone marrow involvement and M spike .....

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2. **All of the following statements about TRM in patients with AL undergoing autotransplantation are true, except one. Indicate the incorrect answer:**
  - a) Is exceedingly high, between 10–20% .....
  - b) Is related to increased level of pro-brain natriuretic peptide (NT-proBNP) .....
  - c) Is correlated with the heavy chain immunoglobulin idiotype of associated monoclonal gammopathy (IgG, IgA, IgM) .....
  - d) Correlates with the number of involved organs .....

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3. **Concerning response after autotransplant, which of the following is the correct answer?**
  - a) Haematologic response assessment is based on serum and urine immunofixation and serum free light chain measurement .....
  - b) Organ responses can be observed in many patients who do not achieve a significant haematologic response .....
  - c) Long-term survival is similar in patients achieving a complete response and those who obtain a partial response .....
  - d) Organ response are always observed in the early period post-transplant, i.e., no longer than 3 months .....

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4. **Which of the following complications can be observed in AL patients undergoing autotransplant?**
  - a) Frequent gastrointestinal bleeding .....

- b) DMSO-triggered cardiac arrest .....
- c) G-CSF induced respiratory failure during mobilisation .....
- d) All the previous have been reported in this setting .....

**5. Which of the following answers is not appropriate for describing outcome after autotransplant in AL patients?**

- a) Long-term follow-up shows a significant proportion of long-term survivors, between 50–60% .....
- b) Relapse rate in patients achieving CR is relatively low, <25% at 5 years .....
- c) Prospective randomised studies comparing the outcome of patients undergoing autotransplant with standard therapy demonstrate a clear benefit in patients receiving intensive therapy .....
- d) Outcome of patients that do not achieve at least a partial response after transplant is poor .....

## NOTES