

## ORIGINAL ARTICLE

# Long-term outcome of high-dose melphalan and autologous stem cell transplantation for AL amyloidosis

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**Light chain (AL) amyloidosis is the result of a clonal plasma cell expansion, in which amyloidogenic monoclonal light chains deposit in various tissues resulting in organ dysfunction and organ failure. The median survival of patients with AL amyloidosis without therapy is 10–14 months. Several phase II studies report haematological and clinical remission in up to 50% of patients after high-dose melphalan and autologous stem cell transplantation. We analysed retrospectively the long-term outcome of 19 patients treated in this way between August/1996 and December/2001. We observed a relatively high treatment-related mortality of 26%, but 12 patients (63%) were high-risk candidates. Eight patients (42%) surviving longer than 100 days achieved haematological remission and long-term survival, whereas 6 (32%) obtained no clear benefit from high-dose therapy. However, 62% of patients survived beyond 2 years and the median survival from transplant was 48 months (range 0–104 months).**

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## Introduction

AL (amyloid light chain) amyloidosis is a result of clonal plasma cell disorder with an incidence of five to 13 persons per million per year.<sup>1</sup> It is the most common and most severe form of systemic amyloidosis. The monoclonal light chains form fibrils that deposit and accumulate in tissues such as the kidney, heart, gastrointestinal tract, liver or autonomic nervous system resulting in organ dysfunction and failure.<sup>2</sup> Without therapy the median survival is 10–14

months from diagnosis.<sup>1,3</sup> Patients with predominantly cardiac involvement have lower median survivals at <5 months.<sup>1,3</sup> The standard treatment for AL amyloidosis with cyclical oral melphalan and prednisone results in haematological remission in approximately 20–30% of patients, slows disease progression and increases the median survival from 13 to 17 months.<sup>4–6</sup> In a recently published study, oral melphalan combined with high-dose dexamethasone (M-Dex) produced better haematological (67%) and organ function (48%) responses indicating that this schedule may be superior to the former melphalan and prednisone.<sup>7</sup> Owing to new treatment options and better supportive care the outcome after conventional chemotherapy in AL amyloidosis has improved since 1990 with an increase in survival to 29 months.<sup>8</sup> However, high-dose melphalan and autologous stem cell transplantation (HDM-ASCT) has been considered an efficient therapeutic approach since promising treatment results were reported in the last 10 years.<sup>9–11</sup> The procedure appears to prolong survival if haematological remission of the plasma cell disease can be achieved, which is possible in up to 50% of patients but is associated with high mortality rates of 15–40%.<sup>11–14</sup> Remarkably, the first prospective randomized study comparing HDM-ASCT with oral melphalan and dexamethasone did not demonstrate statistical difference in haematological response, organ function response or survival between the two treatment modalities in a multicentric setting.<sup>15</sup> On the other hand, a case control study showed a survival advantage for the HDM-ASCT patient group.<sup>16</sup> Therefore, it remains controversial at present, whether one of the two treatment approaches – oral conventional chemotherapy or HDM-ASCT – is superior. Only a few studies focus on long-term survival beyond 3 years from after HDM-ASCT.<sup>14</sup> We analysed treatment data in a series of patients from the Hammersmith Hospital, London, in whom the median survival now reaches 4 years.

## Patients and methods

### Patients

Between August/1996 and December/2001, we treated 19 patients with systemic AL amyloidosis by HDM-ASCT. All the patients were referred for a full assessment and

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evaluation of eligibility to undergo HDM-ASCT to the National Amyloidosis Centre, initially at the Hammersmith Hospital and later at the Royal Free Hospital, London. To estimate the extent of organ involvement, disease history, physical examination and the following investigations were performed:  $I^{123}$  – labelled serum amyloid P (SAP) scintigraphy,<sup>17</sup> electrocardiogram (ECG), echocardiography (ECHO), chest X-ray, skeletal X-rays, abdominal ultrasound, standardised laboratory blood testing including liver and kidney function, 24 h urine collection with quantitation of total protein and light chain excretion, electrophoresis, immunoelectrophoresis and immunofixation of urine and serum, bone marrow aspiration, bone marrow biopsy and, if appropriate, organ biopsy for histological examination.<sup>18</sup> Some patients underwent functional evaluation of their autonomic nervous system. Cardiac, renal, liver or gastrointestinal involvement were confirmed by clinical diagnostic criteria described previously.<sup>11,13,14</sup> Neurological syndromes included symptoms or signs of peripheral sensory neuropathy, motor neuropathy or autonomic neuropathy associated with orthostatic hypotension. Organs with evidence of amyloid disease involvement on either SAP scan or echocardiography or organ biopsy or appropriate organ system examination (neuropathy assessment) were counted to establish the number of organs involved at diagnosis. Patients were considered eligible for HDM-ASCT if they met the following inclusion criteria: age between 18 and 65 years, performance status 0–2 according to World Health Organisation (WHO) criteria and ventricular ejection fraction >30%. Impaired renal function was not a reason for exclusion.

#### *Stem cell collection and transplantation*

Stem cells were collected from the peripheral blood using granulocyte colony-stimulating factor (G-CSF: Filgrastim, Amgen, UK or Lenograstim, Chugai Pharma, UK) at a dose of 10 µg/kg daily for 5 days or at a dose of 5 µg/kg daily with preceding cyclophosphamide or etoposide chemotherapy. A minimum of  $2.0 \times 10^6$  CD34+ cells per kg body weight was required to proceed with transplant. Patients received intravenous HDM at a dose of 200 mg/m<sup>2</sup> or at modified doses in the presence of renal or cardiac dysfunction. Autologous stem cells were infused 48 h after the administration of HDM.

#### *Treatment response and outcome evaluation*

The primary outcome measure was survival. Patients were assessed for therapy-related toxicity, for haematological and clinical response at 3, 6 and 12 months after HDM-ASCT and annually thereafter. At each evaluation clinical examination and laboratory testing of serum and urine (24 h urine collection) were performed including electrophoresis, immunoelectrophoresis, immunofixation and serum-free light chain ratio assessment. Serum amyloid P scan was performed prior to ASCT and 12 months after ASCT.

#### *Haematological and clinical response criteria*

The definition of haematological response to transplant was adapted from that published for multiple myeloma.<sup>19</sup>

Complete haematological response (CR) required the absence of persistent plasma cell disease in the bone marrow, that is, <5% of plasma cells without light chain restriction and no evidence of persistent monoclonal gammopathy detectable by immunoelectrophoresis and immunofixation in serum or urine. Partial haematological response (PR) was defined as 50% loss of serum or urine monoclonal protein in case of still detectable monoclonal plasma cell disease. Serum-free light chain ratio measurements were included into remission assessment according to recently published response criteria.<sup>20</sup> Progression, stabilisation or regression of amyloid deposits were assessed by  $I^{123}$  – labelled SAP scintigraphy at 12 months post ASCT. Clinical responses were defined for each involved organ system. Response of cardiac, renal, gut or liver disease was defined as described before<sup>11–14</sup> and according to recently published response criteria.<sup>20</sup> Relapses were defined according to haematological and organ response criteria.<sup>20</sup>

#### *Statistical analysis*

The survival of patients post transplant was estimated by Kaplan–Meier analysis and depicted by Kaplan–Meier survival plots. Patient groups were compared using a log-rank test. *P*-values reflected two-sided test results, and those <0.05 were defined as statistically significant. Factors that might influence outcome<sup>9,11–14</sup> were analysed using univariate analyses and included age, organ amyloid load defined by SAP scan at diagnosis, total number of involved organs as defined above, type of predominant organ involvement, initial renal function, chemotherapy prior to HDM-ASCT, time from diagnosis to HDM-ASCT and melphalan dose.

## **Results**

#### *Patient characteristics*

Nineteen patients with AL amyloidosis treated by HDM-ASCT at the Hammersmith Hospital, London, between August/1996 and December/2001 were included in the analysis. None of the patients had multiple myeloma with skeletal involvement. Seventeen patients had a monoclonal gammopathy without evidence of multiple myeloma.  $I^{123}$  – labelled SAP scintigraphy was performed in all patients and showed large amyloid load in three, moderate in six and low in 10 patients. In 17 patients, AL amyloidosis was confirmed histologically by kidney (10), gut (4), liver (1), lung (1), or myocardial (1) biopsy. In two patients with polyneuropathy as the leading organ manifestation, no organ biopsy was performed. Symptomatically predominant kidney involvement was the most common manifestation of amyloidosis in 10 patients. Predominant cardiac involvement was present in three patients. In 12 patients more than two organs were involved. According to risk criteria for ASCT in AL amyloidosis based on the number of organs involved,<sup>11</sup> 12 patients were poor and seven were intermediate or good risk candidates. For further details see Tables 1 and 2.

**Table 1** Patient characteristics at diagnosis and treatment summary

	Leading organ	SAP scan amyloid load at diagnosis	Number of involved organs	Risk score <sup>a</sup>	Therapy before HDM	Time from diagnosis to ASCT (Months)	Response of clonal protein at 6–12 months from ASCT	FLC Response at 6–12 months from ASCT	SAP scan at 12 months from ASCT	Events	Time from ASCT to relapse (Months)	Subsequent therapy	Follow-up after ASCT (Months)	Survival	Cause of death
1	Heart	Large	6	Poor	None	4	NA	NA	NA	TRM			1.3	Dead	MOF
2	Heart	Low	2	Interm	Heart transplant	17	CR	CR	Regression				100	Alive	
3	Lung	Low	3	Poor	6 VAD	17	CR	CR	Regression	Relapse	106		110	Alive	
4	Liver	Large	4	Poor	6 VAD	29	CR	CR	Regression				93	Alive	
5	Kidney	Moderate	3	Good	None	9	PD	No response	Progression			HD	20	Dead	Progress
6	Kidney	Moderate	2	Poor	None	16	PD	No response	Static			None	83	Dead	Progress
7	Kidney	Low	1	Good	None	12	CR	CR	Regression	Relapse	84	CTD	82	Alive	
8	Neuropathy	Low	3	Good	8 MP	60	NA	NA	NA	TRM			0.5	Dead	Sepsis
9	Gut	Low	5	Poor	None	2	NA	NA	NA	TRM			0	Dead	Arrhythmia
10	Kidney	Low	4	Poor	None	3	NA	NA	NA	TRM			0.6	Dead	Sepsis
11	Kidney	Low	1	Good	1 C-VAMP	5	PR	CR	Regression	Relapse	46	2. ASCT	62	Dead	Sepsis
12	Kidney	Low	2	Poor	6 Cyclo, 3 VAD	47	CR	CR	Regression				77	Alive	
13	Heart	Moderate	4	Poor	Heart transplant	18	PD	No response	Progression			Oral Cyclo	21	Dead	Progress
14	Kidney	Low	2	Good	3 C-VAMP	23	PR	PR	Regression	Relapse	36	2. ASCT, CTD	72	Alive	
15	Neuropathy	Moderate	5	Poor	3 MP, 6 Z-Dex	23	PD	No response	Static			Thalidomide Dexamethasone HD	57	Dead	Pneumonia
16	Kidney	Moderate	4	Poor	3 VAD	9	PD	No response	NA				7	Dead	Progress
17	Kidney	Moderate	3	Poor	None	7	NA	NA	NA	TRM			0.5	Dead	Brain bleed
18	Gut	Large	4	Poor	None	18	SD	No response	Regression			VAD Thalidomide	48	Alive	
19	Kidney	Low	2	Interm	None	10	PR	No response	Regression	Relapse	54	HD, CTD	42	Alive	

Abbreviations: HDM: high-dose melphalan; ASCT=autologous stem cell transplantation; VAD=vincristine, adriamycin, dexamethasone; MP=melphalan, prednisolone; Z-Dex=idarubicin, dexamethasone; C-VAMP=cyclophosphamide, adriamycin, prednisolone; Cyclo=cyclophosphamide; CTD=cyclophosphamide, dexamethasone, thalidomide; TRM=treatment-related mortality; FLC=free light chains; CR=complete remission; PR=partial remission; SD=stable disease; PD=progressive disease; MOF=multi-organ failure; SAP=<sup>125</sup>I-labelled Serum amyloid P scintigraphy; HD=haemodialysis; NA=not available.

<sup>a</sup>Risk score according to Comenzo and Gertz 2002.<sup>11</sup>

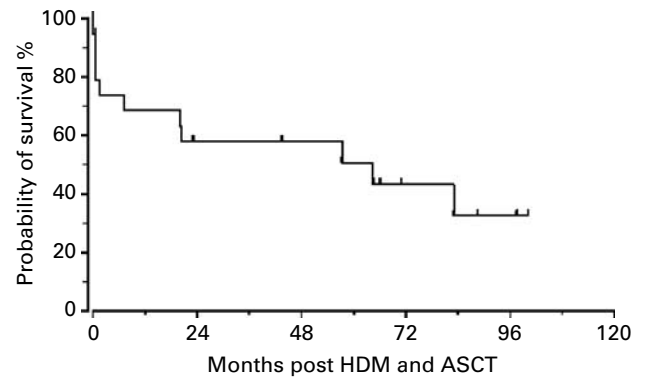
**Table 2** Summary of patient characteristics, laboratory results prior to high-dose melphalan and treatment details

<i>Age</i>		
Median (range) in years		51 (40–63)
<i>Gender</i>		
Male/female		12/7
<i>Light chain</i>		
Kappa/lambda		5/14
<i>Serum creatinine</i>		
Median (range) in $\mu\text{mol/l}$		93 (53–313)
<i>Serum urea</i>		
Median (range) in mmol/l		5.8 (2.3–13.7)
<i>Urine protein</i>		
Median (range) in g/day		5.2 (0.1–20.8)
<i>Creatinine clearance</i>		
Median (range) in ml/min		76 (18–162)
<i><math>\beta 2</math> microglobuline</i>		
Median (range) in mg/l		2.05 (1.2–10.1)
<i>MUGA LVF</i>		
Median (range) in %		58 (31–73)
<i>Melphalan dose</i>		
200 mg/m <sup>2</sup>		9
140 mg/m <sup>2</sup>		4
100 mg/m <sup>2</sup>		5
45 mg/m <sup>2</sup>		1
<i>Infused cell dose <math>\times 10^6/\text{kg BW}</math></i>		
Median (range)		3.45 (1.96–11.28)

Abbreviations: MUGA LVF = radionuclide multiple-gated acquisition scanning left ventricular function; BW = body weight.

### Treatment

Before HDM-ASCT, eight patients were treated with cyclic chemotherapy with either vincristine, adriamycin, dexamethasone (VAD) ( $n=4$ ), idarubicin, dexamethasone (Z-Dex) ( $n=1$ ), cyclophosphamide, vincristine, adriamycin, prednisone (C-VAMP) ( $n=2$ ) or melphalan, prednisone (MP) ( $n=1$ ), the other 11 patients proceeded to stem cell mobilisation and transplant without prior therapy. The median time from diagnosis to HDM-ASCT was 16 months (range 2–60 months). Stem cells were mobilised after cyclophosphamide (4 g/m<sup>2</sup>) and G-CSF in three patients, after etoposide (1.6 g/m<sup>2</sup>) and G-CSF in one patient and after G-CSF alone in 14 patients. In one patient a bone marrow harvest was performed. A median of  $5.2 \times 10^6$  CD34+ cells per kg body weight were collected (range 1.96–50.17  $\times 10^6$ ). In the patient who required the bone marrow harvest the cell dose was  $4.99 \times 10^8$  total nucleated cells per kg body weight. The details of melphalan dose and infused stem cell dose are summarized in Table 2. Five patients died during the first 100 days post transplant equivalent to a probability of day 100 TRM of 26%. Of those five patients, four were classified as poor risk and one as good risk according to the Comenzo criteria,<sup>11</sup> resulting in a TRM of 33% in the poor risk group and 14% in the intermediate/good risk patients. The causes of death

**Figure 1** Probability of survival after months post high-dose melphalan (HDM) and autologous stem cell transplantation (ASCT).

were sepsis in two patients (at days 15 and 19), brain haemorrhage in one patient (day 15) and cardiac arrhythmia in one patient (day 1). The remaining early death was due to multiorgan failure on day 42 despite good peripheral blood count recovery. All 15 patients who survived longer than 28 days from ASCT engrafted and reached neutrophil counts  $>0.5 \times 10^9/\text{l}$  and platelet counts  $>50 \times 10^9/\text{l}$  at medians of 15 (range 6–25) and 21 days (range 9–32), respectively.

### Treatment response

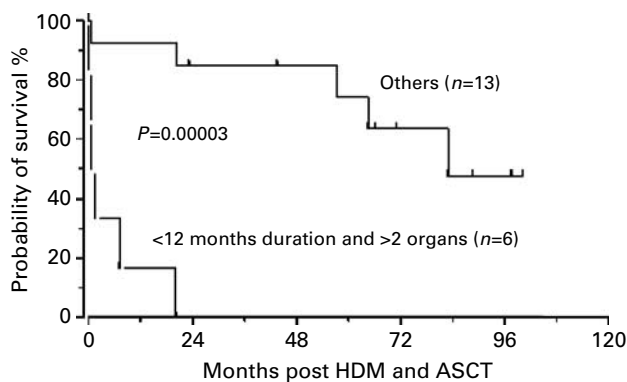
**Survival.** The median survival from HDM-ASCT was 48 months (range 0–104 months). 73% of patients survived more than 1 year and 62% were alive 2 years after transplant. However, survival by 6 years had fallen to 37% due to disease relapse and/or progression (Figure 1). In univariate analyses the involvement of more than two organs and a short disease duration from diagnosis to HDM-ASCT were the only negative predictors for survival (Table 3) and the combination of these two factors identified a very poor risk group of patients (Figure 2). Age, type of predominant organ involvement, SAP scan amyloid load at diagnosis, serum creatinine at time of HDM-ASCT and chemotherapy prior to HDM-ASCT did not impact on survival (Table 3).

**Haematological and clinical response rates.** Fourteen patients who survived more than 100 days were evaluable for haematological and clinical responses.

Eight patients (57% of the evaluable 14 and 42% of the original 19 patients) achieved haematological remission at 12 months: five had a complete remission and three a partial remission based on immunoelectrophoresis and/or serum-free light chain ratio. In all eight patients regression of organ amyloid load by SAP scintigraphy and either improvement or stabilisation of organ function were found at 12 months assessment. Disease relapse was diagnosed based on clonal protein and/or serum-free light chain ratio and occurred in five patients after 36, 46, 54, 84 and 110 months from HDM-ASCT. Two patients received a second ASCT for disease relapse. The others were treated with systemic low-dose chemotherapy. All but one patient in this group remain alive at a

**Table 3** Univariate analysis of factors with a possible impact on survival after high-dose melphalan (HDM) and autologous stem cell transplantation (ASCT)

	Mean survival in months (95% confidence interval)	Log-rank test P-value
<i>Age at diagnosis</i>		
< 50 years (n = 9)	52.9 (24–82)	0.72
> 50 years (n = 10)	49.2 (24–74)	
<i>Number of involved organs</i>		
1–2 organs (n = 7)	89.4 (77–101)	0.01
> 2 organs (n = 12)	30.1 (9–52)	
<i>SAP scan amyloid load at diagnosis</i>		
Small (n = 10)	66.1 (38–94)	0.12
Medium/large (n = 9)	47.0 (13–60)	
<i>Leading organ</i>		
Heart (n = 3)	40.6 (0–89)	0.99
Kidney (n = 10)	51.8 (28–75)	
Liver and gut (n = 3)	28.9 (6–52)	
Others (n = 3)	51.8 (33–72)	
<i>Serum creatinine at HDM</i>		
< 100 $\mu\text{mol/l}$ (n = 10)	51.0 (22–81)	0.82
> 100 $\mu\text{mol/l}$ (n = 9)	53.9 (30–77)	
<i>Treatment before HDM</i>		
No chemotherapy (n = 11)	46.8 (21–73)	0.49
Chemotherapy (n = 8)	63.1 (37–90)	
<i>Duration of disease prior to HDM</i>		
< 12 months (n = 9)	28.8 (6–52)	0.046
> 12 months (n = 10)	72.7 (50–94)	

Abbreviations: SAP scan =  $I^{125}$  - labelled Serum amyloid P scintigraphy.**Figure 2** Probability of survival after months from high-dose melphalan (HDM) autologous stem cell transplantation (ASCT) by duration of disease and number of involved organs.

median follow-up of 80 months (range 42–110 months, see Table 1).

Six patients (43% of the evaluable 14 and 32% of the original 19) did not show haematological response, displaying stable or progressive plasma cell disease at 12 months assessment. Despite the lack of haematological response, stabilisation of systemic amyloid load in SAP

scintigraphy was observed in two and SAP load regression in one patient. As result of progressive renal failure two patients required haemodialysis. Three patients were treated with second and third-line chemotherapy regimens. The median follow-up in this group is 35 months (range 7–83 months, see Table 1).

## Discussion

Untreated systemic AL amyloidosis is a progressive and fatal disease in almost all cases.<sup>1</sup> High-dose melphalan coupled with autologous stem cell support is used since feasibility was confirmed in early reports,<sup>9,10</sup> but until now opinions on its role in AL amyloidosis are controversial.<sup>8</sup> Procedure-related mortality is high at 14–30%,<sup>11–14</sup> and symptomatic improvement and recovery of organ function are usually slow. Nevertheless, approximately 50% of patients achieve haematological remission of the plasma cell disease.<sup>11–14</sup> Dispenzieri *et al.*<sup>16</sup> performed a retrospective matched pair analysis of patients treated with low-dose cyclic melphalan and prednisone chemotherapy and patients treated with HDM-ASCT. They demonstrated a significantly better survival rate for the group of patients treated with high-dose therapy. However, results of the only randomised trial so far performed in 100 patients did not show superior outcome after HDM-ASCT in comparison to M-Dex.<sup>15</sup> A study by Sanchorawala *et al.*<sup>21</sup> concludes that initial treatment with melphalan and prednisolone does not improve the outcome after HDM, but that treatment delay can have a negative impact on survival.

We report here on HDM-ASCT treatment in a group of 19 patients with AL amyloidosis treated in a single transplant centre. In this group, 74% of patients survived longer than 100 days from transplant and the haematological remission rate was 42% which is comparable with previous findings.<sup>11–14</sup> Out of 13 patients eligible for SAP scan assessment at 12 months nine patients (47% of initially treated 19) had regression of their amyloid load as shown by the SAP scan. Amyloid regression was observed even in patients who did not achieve complete haematological remission and in some patients without haematological response stable SAP appearance was found. These findings suggest that – contrary to current assumptions – not only stabilisation but even regression of amyloid deposits in several organs is possible if patients achieve haematological response to treatment. We conclude from our findings that high dose chemotherapy with melphalan has the potential to suppress plasma cell proliferation and permit degradation of amyloid deposits in a proportion of patients. A limitation of our study is its retrospective design and the analysis of only one treatment approach. The prospective randomized French study<sup>15</sup> did not prove superiority of HDM-ASCT compared with M-Dex in terms of haematological response, organ function response or survival so that further prospective trials are needed.

High-dose melphalan and autologous stem cell transplantation-related mortality in our patient group was 26%, which is comparable to data reported previously.<sup>11–14,21–23</sup> The proportion of patients with involvement of more

than two organs or with poor initial organ function was relatively high at 63%. Indeed, the TRM was particularly high in our poor risk patients (33%), but was appreciably lower in the intermediate and good risk patients (14%). In our group, the only parameters with prognostic impact on survival were extensive organ involvement of more than two organs and time since diagnosis of less than 12 months. Patient age, type of predominant organ involvement, amyloid load estimated by SAP scan, serum creatinine or chemotherapy before transplant did not have an impact on survival. Other authors similarly reported the negative impact of cardiac involvement and involvement of more than two organs.<sup>11,12-14,24</sup> In our patient group the poor survival of patients treated within 12 months from diagnosis probably reflects the selection of poor risk patients as candidates for urgent HDM-ASCT. In contrast, patients who were eligible for ASCT after more than 12 months from diagnosis may have had less aggressive disease biology. Despite previous findings<sup>21</sup> it remains unclear, whether AL amyloidosis patients should be treated with ASCT shortly after diagnosis or after pre-treatment with low-dose chemotherapy. Further prospective studies taking into account different risk groups and comparing HDM-ASCT early in the course of the disease with HDM-ASCT after initial chemotherapy are needed in this field. Unfortunately, poor risk patients with extensive organ involvement are unlikely to do well with conventional therapy and some younger individuals may still elect for transplant. Undoubtedly, better selection of patients most likely to benefit from high-dose therapy will result in decreased TRM and improved survival.

Overall survival at 2 years was encouraging at 62% and seven out of eight patients who achieved a haematological response remain alive. On the other hand, we saw late relapses and deaths after 2 years from HDM-ASCT. As the outcome is generally promising for patients surviving the first 100 days from HDM-ASCT, future studies should focus on strategies to prevent and treat disease relapse and progression in patients who do not respond to or relapse after high-dose chemotherapy and ASCT. New strategies – particularly with the use of proteasome inhibitors or immunomodulatory agents – may prove valuable treatment options for these patients.

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