Stringent patient selection improves outcomes in systemic light-chain amyloidosis after autologous stem cell transplantation in the upfront and relapsed setting

Autologous stem cell transplantation (ASCT) is an effective treatment for amyloid light-chain (AL) amyloidosis leading to both deep and durable clonal responses with excellent median overall survival of over five years with those attaining a complete hematologic response and surviving relapse free for over eight years.[1] Concerns about high transplant-related mortality (TRM), up to 32%[2] as previously reported by our group, have limited the use of ASCT in many countries, including the UK. More recently, with a clearer understanding of pre-transplant risk factors including the impact of cardiac involvement, patient selection criteria have been greatly refined, leading to a marked improvement in TRM[1,3] in centers of experience. However, despite improvements in TRM, particularly the incidence of dialysis-dependent renal failure (previously estimated to be approximately 3%[4]) remains a poorly studied area of concern.

The timing of transplant, upfront or at relapse, remains an outstanding question in this disease, with limited published data and no prospective trials. There is an ever-increasing patient population treated upfront with highly effective novel chemotherapy regimens which may allow improvement of high-risk patients to the point where transplant becomes feasible or, conversely, encourage good risk patients to defer transplant until the time of relapse.

Here we report the UK experience using ASCT in patients with AL amyloidosis who underwent risk stratification and transplantation in the modern era (January 2003-September 2012). Importantly, we present the first study to examine the timing of high-dose therapy in this disease and report our attempts to establish the risk of end-stage renal failure and the need for long-term dialysis as a consequence of the transplant procedure.

This study reports all patients in the database at the UK National Amyloidosis Centre (NAC) who have undergone ASCT for AL amyloidosis due to underlying plasma cell dyscrasia since the data cut off of the initial UK publication examining high-dose chemotherapy in this disease in the first decade of this century.[2] Since that time, more rigorous patient selection has been put in place (*Online Supplementary Table S1*). In our study, conditioning regimens, dosage and post-transplant supportive care were directed by each treating institution (amongst 21 British Society of Bone Marrow transplantation centers). Confirmation of AL type, characterization of organ involvement as well as both hematologic and organ responses were assessed as per the 2012 criteria.[5] Mayo Cardiac staging was performed on all patients.[6] The rate of permanent dialysis-dependent renal failure post ASCT was also examined. Progression-free survival (PFS) was determined from the date of ASCT until hematologic/organ progression[5] or death. Overall survival (OS) was calculated from both diagnosis and time of ASCT. TRM was defined as death within 100 days of transplant.

Univariate and multivariate analysis was performed to examine for factors predictive of outcome post ASCT. NT-proBNP more than 500 ng/L was chosen since, in our series, it gave the greatest differential in post ASCT OS by log rank test (log rank=9.49; *P*=0.002). The difference between involved and uninvolved free light chains (dFLC) and cardiac high-sensitivity (HS) troponin-T were also examined based on the recently published cut offs with more than 180 mg/L[7] and more than 0.06 ng/L,[8] respectively. Pre-ASCT albumin level was examined with a cut off of 25 g/L, based on previous publications.[9,10]

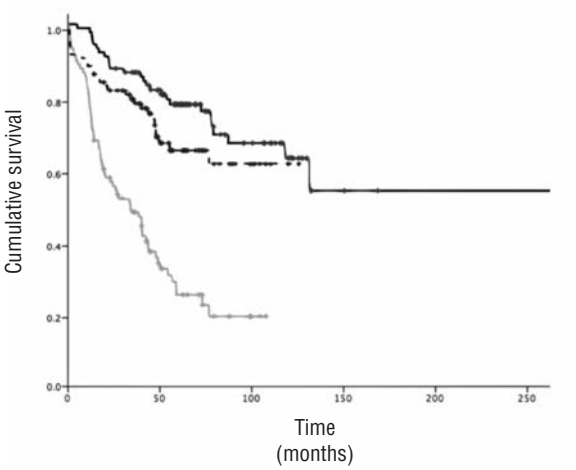

Figure 1. Survival outcomes post high-dose chemotherapy and autologous stem cell transplantation (ASCT) for patients with amyloid light-chain (AL) amyloidosis. These curves reflect the outcome for the whole cohort (n=90). Solid black line shows overall survival (OS) from diagnosis. Dashed black line shows OS from the time of ASCT. Solid gray line reflects progression-free survival (PFS) from the time of ASCT. The median OS from both diagnosis and transplant has not been reached (estimated 5-year survival 77.8%). Median OS from the time of ASCT was not reached (estimated 5-year survival 66.5%). Median PFS for the whole cohort 34.0 months (95%CI: 19.2; 48.8). Survival outcomes analyzed using the Kaplan-Meier method.

Ninety patients were identified who had undergone ASCT during this time period, 33 (38%) of whom had undergone transplantation upfront. Complete patients' characteristics are described in Table 1. All 90 patients were evaluable for clonal response. By intention-to-treat (ITT) analysis, a hematologic response was noted in 69 (77%) patients [CR in 32 (36%) and dFLC-VGPR or over in 52 (58%)]. In those patients treated upfront, 28 (85%) achieved a hematologic response with 22 (67%) achieving dFLC-VGPR or over [CR in 11 (33%)]. In those who received ASCT for relapsed disease, 41 (72%) achieved a hematologic response with 31 (54%) attaining dFLC-VGPR or over [CR in 22 (39%)]. There was no statistically significant difference in overall hematologic response, dFLC-VGPR or over, or CR rates between those transplanted upfront *versus* those transplanted at relapse (*P*=0.20, 0.50 and 0.36, respectively). These responses, especially CR/VGPR rates, are comparable to those that have been described previously with ASCT,[1,11,12] and possibly superior to those reported with the more widely used low-dose chemotherapy regimens such as melphalan and dexamethasone,[13,14] and cyclophosphamide, thalidomide and dexamethasone (CTD),[15] as well as the recent experience with lenalidomide containing regimens.[16-21]

Renal responses were noted in 21 (33%) and liver responses in 6 (7%) of those patients with these organs involved at baseline. Out of 17 patients eligible for assessment of cardiac responses (base-line NT-proBNP >650 ng/L),[5] responses were observed in 6 (35%). With a durable dFLC-VGPR or over, these organ responses may continue to improve.

The median follow up was 47.5 months (m) from ASCT and 69.2 m from diagnosis. Consistent with recently published datasets, OS as well as PFS from diagnosis and from

ASCT are excellent (Figure 1).[1,12] The median PFS was approximately four years for those attaining dFLC-VGPR or over. This is broadly similar to the median event-free survival of approximately five years for patients achieving a CR/dFLC-VGPR recently reported by the Boston group.[1,9] The Boston cohort was a landmark analysis of patients assessable for response at 12 months, which is a key difference from the current cohort analyzed on an ITT basis, likely accounting for the difference in the PFS between the series.

Table 1. Patients' characteristics based on timing of transplant.

Clinical characteristic	All	ASCT upfront (n=33)	ASCT at relapse (n=57)	P
Median age (years)	58.3 (30-69)	58.3 (40-69)	58.1 (30-68)	0.61
Sex (female, %)	47.8	51.2	45.6	0.56
ECOG > 1 (%)	6.9	3.0	9.3	0.26
Monoclonal protein type (%)				
IgG	44.4	48.5	42.1	0.56
IgA	7.8	9.1	7.0	0.72
IgD	2.2	3.0	1.8	0.69
IgM	1.1	3.0	0.0	0.19
Light chain only	44.4	36.4	49.1	0.24
Lambda (%)	64.4	75.8	57.9	0.08
Median dFLC (mg/L)	200.2 (2.3-26697)	177.4 (2.5-26697)	237.7 (2.3-5993)	0.43
dFLC>180 mg/L (%)	51.7	50.0	52.7	0.14
Organ involvement (%)				
Renal	40.0	69.7	71.9	0.82
Cardiac	24.4	27.3	22.8	0.64
Hepatic	13.3	6.1	12.3	0.12
Peripheral nerves	12.2	15.2	10.5	0.52
Autonomic nerves	4.4	3.0	5.3	0.62
Gastrointestinal	8.9	9.1	8.8	0.96
Soft tissue	33.3	30.3	33.3	1.00
Other	18.9	18.2	15.8	0.32
>2 organs involved (%)	22.2	24.2	21.1	0.73
Median creatinine (mg/dL)	77.0 (34-654)	72.0 (34-162)	81.0 (34-654)	0.19
Median eGFR (mL/min)	88.0 (0-107)	94.0 (33-106)	87.0 (0-107)	0.49
eGFR <45 mL/min (%)	9.3	9.4	9.3	0.99
Median 24-h urine protein (grams)	1.3 (0-12.1)	1.8 (0.1-11.6)	1.2 (0-12.1)	0.77
Nephrotic range proteinuria (%)	37.8	42.4	35.1	0.49
Albumin <25 g/L (%)	11.6	10.3	14.9	0.62
Median albumin (g/L)	39.0 (17-49)	36.2 (17-48)	36.9 (19-49)	0.62
Median alkaline phosphatase (U/L)	75.0 (43-306)	72.0 (43-284)	76.0 (45-306)	0.54
Median ventricular wall thickness (mm)	10.8 (8-16)	10.3 (9-16)	11.0 (8-15)	0.43
Median ejection fraction(%)	60.5 (50-72)	60.0 (50-68)	61.0 (56-72)	0.41
Median NT-proBNP (ng/L)	258.5 (25.4-5033)	360.2 (25.4-5033)	224.6 (33.9-3932)	0.11
NT-proBNP>500 ng/L (%)	25.6	36.7	21.4	0.19
Median HS-Troponin T (ng/mL)	0.01 (0.003-0.091)	0.01 (0.003-0.091)	0.01 (0.003-0.091)	0.15
HS-Troponin T >0.06 (%)	3.3	6.5	1.9	0.29
Mayo Cardiac Stage (%)				
I	55.6	42.4	63.2	0.03
II	28.9	42.4	21.1	0.03
III	5.6	6.1	5.3	0.89
Not available	10.0	9.1	10.5	0.10
Induction pre-ASCT (%)*	38.9	75.6	17.5	<0.001
Disease status for relapsed patients (%)				
Relapse	–	–	82.5	–
Refractory	–	–	17.5	–
Conditioning regimen (%)				
Melphalan 100 mg/m^2	10.0	15.2	10.5	0.22
Melphalan 140 mg/m^2	11.1	9.1	12.3	0.64
Melphalan 200 mg/m^2	44.4	48.5	42.1	0.56
Melphalan dose uncertain	34.4	27.3	35.0	0.28

Patients undergoing ASCT as a consolidative procedure after initial low-dose therapy.

These data provide further insight into the impact of ASCT on outcome based on the timing of the transplant. The median follow up from ASCT in those transplanted upfront *versus* relapse was 45.0 m and 48.4 m, respectively. There was no significant difference in PFS or OS from transplant based on timing of transplant (Figure 2). Additionally, there was no difference in OS from diagnosis (estimated OS 69% and 68% at 8 years; *P*=0.7). These are important observations and support the notion that ASCT may have a role in improving the long-term outcomes of even high-risk patients, assuming one can appropriately treat them initially with low-dose regimens aimed at improving their organ function. This had been demonstrated previously and may be particularly true when initial therapy is pursued with more potent novel agent containing regimens.[22] A prospective trial focusing on the timing of transplant in AL amyloid is warranted to assess this and provide some definitive conclusions.

With a TRM of 6.8% for the whole cohort, we show compelling evidence of a dramatic decrease in early death; this is comparable to previously published UK data and is in keeping with other contemporary transplantation series.[1,23] This is most likely driven by a low proportion of patients with advanced cardiac disease (Mayo stage III: only 7%). Moreover, only one patient had a NT-proBNP more than 5000 ng/L and 3 had a Troponin more than 0.06 ng/mL, both risk factors identified by the Mayo group as being major predictors of poor outcome with ASCT.[24] While recognizing the biases in this series due to the rigorous patient selection, we attempted to identify variables that may help stratify these patients further. While, unsurprisingly, elevated NT-proBNP predicted for worse long-term OS, no factor was predictive of early death in this highly selected cohort. This observation is reassuring as it indicates that transplant centers in the UK are rigorously applying the selection criteria. The reduction in TRM demonstrated here will reduce concerns raised during previous experiences.

Autologous stem cell transplantation is still under-used in the UK. Although this was not the focus of the current study, due to the lack of retrospective data on the proportion of patients in the UK who qualified for an ASCT but who did not proceed with the treatment in the study period, only 10 of 714 patients enrolled in a recent prospective observational study (ALChemy) between 2009 and 2013 underwent upfront ASCT although 15% had met criteria for transplantation *(AD Wechalekar, unpublished data, 2014)*.

Similarly, it was reassuring to see that the rate of renal complication was very low. Only 3 patients required long-term dialysis attributable to the ASCT (3.3%). Given the extremely low event rate, one cannot make any definitive comment on risk factors for dialysis. However, our data suggest that pre-transplant nephrotic syndrome may be a predisposing factor for needing long-term dialysis post ASCT (on univariate analysis: Pearson χ^2 test=5.6; *P*=0.018), consistent with previous publications.[25,26] While not necessarily an absolute contraindication to proceeding with ASCT, it may influence the timing of the high-dose therapy in the light of the fact that the post-ASCT PFS and OS are similar upfront or at relapse. This has to be weighed against the risk of renal progression should there be poor response to or complications during upfront therapy which would thereby make them ineligible for ASCT.

In summary, the data presented here add to the growing body of literature supporting the ongoing use of ASCT in patients with AL amyloidosis. It leads to deep and, most importantly, durable responses in a disease where the depth of clonal control directly influences long-term organ function and survival. Importantly, the timing of high-dose chemotherapy does not seem to affect post-transplant outcome suggesting an expanded role for this modality of therapy. Key to its success is the rigorous adherence to modern patient selection criteria. Marked national-level improvements can be achieved using these approaches, as exemplified in this update of the treatment modality in the UK. The next frontier to further improve complete responses will be the incorporation of novel agents directly into the transplant sequence.

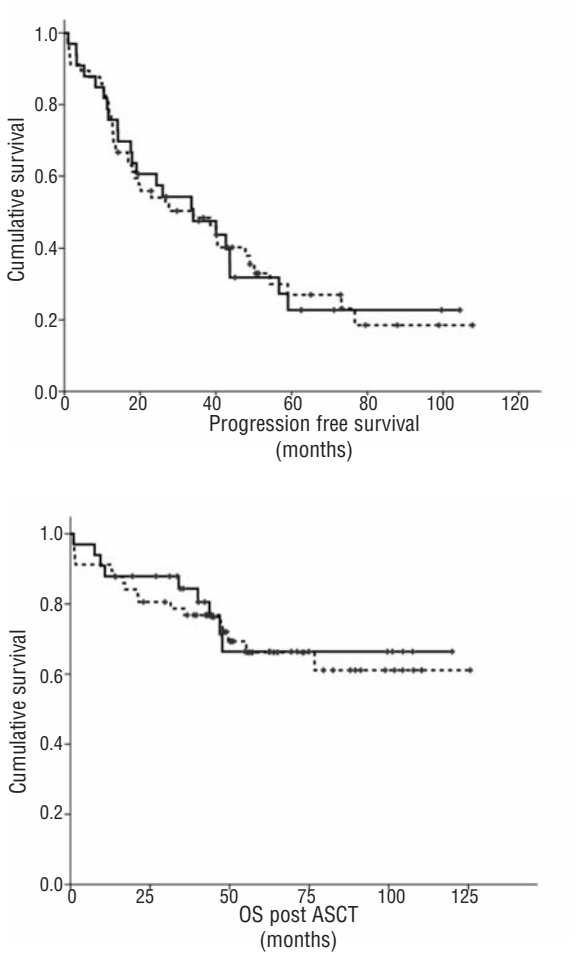

Figure 2. **Survival outcomes post high-dose chemotherapy and autologous stem cell transplantation (ASCT) for patients with amyloid light-chain (AL) amyloidosis by timing of transplant. Comparisons were made based on timing of transplant with the solid line reflecting upfront (n=33) transplantation and the dashed line representing transplants for relapsed disease (n=57). Overall survival (OS) from transplant (a) and progression-free survival (PFS) from transplant (b) were examined. The estimated 5-year OS for those transplanted upfront *versus* relapse were 66% and 69%, respectively (*P*=0.81). The median PFS for those transplanted upfront *versus* relapse were 34 months (95%CI: 14.0; 54.0) and 34 months (95%CI: 11.6; 56.6), respectively (*P*=1.0). Survival outcomes were analyzed using the Kaplan-Meier method with comparisons made using the log rank test. All *P*-values were two-sided. *P*<0.05 was considered significant.**

Christopher P. Venner,[1,2] Julian D. Gillmore,[1] Sajitha Sachchithanantham,[1] Shameem Mahmood,[1] Thirusha Lane,[1] Darren Foard,[1] Murielle Roussel,[3] Lisa Rannigan,[1] Simon DJ Gibbs,[1,4] Jennifer H Pinney,[1] Carol J. Whelan,[1] Helen J. Lachmann,[1] Philip N. Hawkins,[1] and Ashutosh D. Wechalekar[1]

[1]National Amyloidosis Centre, University College London Medical School, UK; [2]Cross Cancer Institute, University of Alberta, Edmonton, Canada; [3]Hématologie Clinique, CHU Purpan, Toulouse, France; and [4]Central Manchester University Hospital, Department of Clinical Haematology, Manchester, UK

Correspondence: a.wechalekar@ucl.ac.uk
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