Long-term outcomes and renal responses following autologous hematopoietic stem cell transplantation for light chain deposition disease: a retrospective study on behalf of the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation

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Abstract

There is little long-term outcome data on the efficacy of autologous hematopoietic stem cell transplantation (ASCT) in light chain deposition disease (LCDD). We identified 51 LCDD patients in the European Society for Blood and Bone Marrow transplantation registry who had undergone upfront ASCT between 1995 and 2021. The median serum creatinine was 280 μmol/L and 45% required renal replacement therapy (RRT) at time of transplant. The melphalan dose was 100 mg/m² in 23%, 140 mg/m² in 55% and 200 mg/m² in 21%. The rate of very good partial response or better improved from 41% pretransplant to 66% at day +100 post-ASCT. In RRT-independent patients, there was a modest improvement in renal function within the first 3 months; the median estimated glomerular filtration rate increased from 44 to 51 mL/min/1.73 m². There was no further change between 3 and 12 months post-ASCT. No patient who was RRT-independent at ASCT became RRT dependent by day + 100 post-ASCT. Median follow-up post-ASCT was 84 months (interquartile range [IQR]: 46-122). At 6-years post ASCT, overall survival was 88% (95% confidence interval [CI]: 78-98) and PFS was 44% (95% CI: 28-60). The 2-year cumulative incidence of relapse and non-relapse mortality was 17% (95% CI: 6-27) and 2% (95% CI: 0-6), respectively. The cumulative incidence of renal transplantation at 4 years after ASCT was 27% (95% CI: 13-41) with renal transplantation performed between 6.3 and 52.9 months post-ASCT (median 24.7 months). ASCT represents a feasible option for LCDD patients even if RRT dependent at time of transplant. Outcomes are favorable with low non-relapse mortality and good long-term overall survival.

Introduction

Light chain deposition disease (LCDD) is a rare disease involving deposition of amorphous non-amyloid monoclonal immunoglobulin light chains (AL), most often κ restricted, along basement membranes.[1-3] It is frequently associated with plasma cell disorders such as multiple myeloma (MM) or other B-cell lymphoproliferative disorders though, sometimes no clonal B-lymphocytes/plasma cells can be identified. LCDD typically involves organs, the kidneys being the cardinal organ involved, but also rarely the heart, liver and peripheral nerves.[1-7]

Therapeutic approaches historically have been adapted from the treatment algorithm followed for MM. Both bortezomib and lenalidomide based regimens have shown encouraging results.[8,9] High-dose melphalan followed by autologous stem cell transplantation (ASCT) has also shown favorable outcomes in few retrospective studies with a limited number of patients focusing on LCDD/heavy chain DD, demonstrating that hematological response along with some organ responses can be achieved.[10-12] However, the role of ASCT remains, on occasion, controversial in this setting, especially as these patients quite frequently demonstrate marked renal impairment, sometimes requiring renal replacement therapy (RRT). Therefore, ASCT toxicity and morbidity in this setting can be a considerable challenge. Of note, successful reversal of renal failure with RRT independence has been previously reported following ASCT in some cases.[13]

We hereby report outcomes from a retrospective, multicentre, European Society for Blood and Bone Marrow Transplantation (EBMT) registry-based study of 51 adult patients with a confirmed diagnosis of LCDD who underwent ASCT, assessing toxicity and efficacy with regard to both hematological and renal responses.

Methods

Study design and patient selection

This was a retrospective, multicenter, registry-based analysis approved by the Chronic Malignancies Working Party of the EBMT. The EBMT is a non-profit, scientific society representing more than 600 transplant centers mainly in Europe. Data are entered, managed, and maintained in a central database with internet access. Each EBMT center is represented in this database. All centers commit to obtain informed consent according to the local regulations applicable at the time in order to report pseudonymized data to the EBMT.

Newly diagnosed LCDD patients who underwent upfront ASCT between 1995 and 2021 were selected from the EBMT database. In addition, we contacted 469 ASCT centers to ask whether any LCDD patients had received ASCT during this period. For patients thus identified, renal biopsy reports were requested from the centers. Submitted renal biopsy reports were checked and verified by two AL amyloidosis-specialized physicians. Inclusion criteria mandated a diagnosis of LCDD made after renal biopsy showing typical glomerular and tubular lesions by light microscopy, immunofluorescence and electron microscopy analysis. The presence of AL amyloidosis was an exclusion criterion as well as other MGRS.

Outcome

The primary endpoint of the study was the cumulative incidence of non-relapse mortality (NRM). Secondary endpoints were overall survival (OS), progression-free survival (PFS) and cumulative relapse incidence (RI), neutrophil and platelet engraftment, renal transplantation, hematological and renal response.

Engraftment

Time to neutrophil engraftment was defined as the first of 3 consecutive days with a neutrophil count $>0.5\times10^9$/L and time to platelet engraftment the first of 3 consecutive days with an unsupported platelet count $>20\times10^9$/L. The use of growth factor was allowed.

Light chain deposition disease hematological response criteria

Disease response to treatment was defined according to the new criteria for response to treatment in AL amyloidosis based on free light chain measurement.[14,15]

Evaluation of renal function

Renal function was assessed by serum creatinine level and estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. Renal response was based on the criteria proposed by the International Myeloma Working group.[16] We did not use the amyloid renal response criteria based on proteinuria.

Outcome after autologous stem cell transplantation

OS was considered to be the time from ASCT to death from any cause, and PFS was the time from ASCT until disease relapse/progression or death, whichever occurred first. NRM was defined as death post-ASCT without relapse/progression.

Statistical analysis

Quantitative data were described by median, interquartile ranges (IQR). Qualitative data were presented by their frequency and proportion, calculated among subjects with no missing values for the corresponding variable. The median follow-up was calculated using the reverse Kaplan-Meier estimator.[17] Both time to neutrophil and time to platelet engraftment were analyzed using the crude cumulative incidence estimator with death as a competing event. OS and PFS were estimated with the Kaplan-Meier method, and cumulative incidence of relapse (CIR) and NRM were estimated using the crude cumulative incidence function to account for the competing event. In order to test for differences between groups the log-rank test was used for OS and PFS and Gray's test was used for RI and NRM. A multistate model was used to give an overview of the probability of events or states after ASCT. We used a non-parametric time inhomogenous Markov model stratified for RRT status at ASCT.[17] All analyses were performed in R version 4.2.2 using 'survival', 'cmprsk' and 'prodlim', 'mstate'[18] and 'lme4' packages.[19]

More details are available in the *Online Supplementary Appendix*.

Results

Baseline patient characteristics at diagnosis

One hundred and thirty-five patients with a registered LCDD diagnosis and an ASCT during 1995-2021 were identified in the EBMT database and renal biopsy reports for these patients were requested. In addition, 469 centers were asked to send renal biopsy reports of any patient with a LCDD diagnosis and an ASCT during this period. Renal biopsy reports were thus received for 63 patients. After checking the reports, a total of 51 patients with a verified LCDD diagnosis from 24 EBMT-registered centers were included in the study (Table 1). For 40 patients additional data was acquired through the data questionnaire. Sixty-three percent were male and the median year of diagnosis was 2011 (IQR, 2009-2016). The underlying plasma cell disorder was MM (62%), smoldering myeloma (8%) and monoclonal gammopathy of unknown significance (MGUS, 30%). Among 38 patients with data available, 16% had evidence of bone lesions. Median bone marrow aspirate plasma cell burden was 10% (IQR, 7.8-20) and serologic immunoglobulin (Ig) isotype (available in 44 patients, 86%) was IgG in 25%, IgA in 2.5%, light chain in 70%, and IgD in 2.5%. Light chain distribution (available in 44 patients, 86%) was κ in 82%, and λ in 18%. Median κ and λ light chain serum concentration were 575 mg/L (IQR, 146-1,095) and 20.4 mg/L (IQR, 11.7-43.5), respectively. Among the 17 patients with cytogenetics available, three patients had a translocation t (11;14) and 1 a deletion of 17p. Among the 40 patients with available data on disease involvement, three patients additionally demonstrated cardiac involvement and two patients hepatic involvement. At diagnosis, median serum creatinine was 233 μmol/L (IQR, 159-467) and the median level of proteinuria was 1,813 mg/24 hours (IQR, 445-5,974). The renal histology was: glomerulosclerosis in 39 patients (76%) with a glomerular involvement ≤50% in 22 (88%) and >50% in three (12%) (quantification available in 25 patients), tubular atrophy in 36 patients (71%) with ≤50% involvement in 12 (63%) and >50% in seven (37%) (quantification available in 19 patients) and interstitial fibrosis in 41 patients (80%) with ≤50% involvement in 18 (69%) and >50% in eight (31%) (quantification available in 26 patients). No crescentic glomerulonephritis was mentioned.

Induction regimen

Among the 44 patients with data available, 42 patients (95%) received an induction regimen prior to ASCT (in 89% bortezomib-based). Induction regimens (available for 41 patients) comprised of: bortezomib and dexamethasone, N=19; bortezomib, thalidomide and dexamethasone, N=5; bortezomib, lenalidomide and dexamethasone, N=6; bortezomib, adriamycin and dexamethasone, N=4; daratumumab and bortezomib-thalidomide-dexamethasone, N=2; bortezomib cyclophosphamide and dexamethasone, N=1; cyclophosphamide, thalidomide dexamethasone, N=1; vincristine, adriamycin and dexamethasone, N=1; bortezomib, melphalan and dexamethasone, N=1; and dexamethasone alone, N=1. A total of four patients had two lines of induction treatment.

Stem cell collection

Stem cell mobilization regimen detail was available in 42 patients (82%). This comprised of granulocyte colony-stimulating factor (G-CSF) in 26 (62%), granulocyte macrophage-CSF (GM-CSF) in two (5%), G-CSF + plerixafor in two (5%), plerixafor alone in one (2%) and cyclophosphamide based in 11 (26%) patients. The number of days of apheresis for collection was 1 in 41 (93%) cases, one patient had two courses of mobilization (each mobilize with G-CSF alone).

Patient characteristics at transplant

Median age at transplant was 55 years (IQR, 49-61) with a median time from diagnosis to transplant of 7.4 months (IQR, 5.5-13.0). Karnofsky performance status was >80 in 79% of the patients; 59% of patients underwent ASCT in 2012 or later. Data on RRT status was available in 38 patients (75%). A total of 17 patients (45%) were undergoing RRT at time of ASCT. Hematological response at ASCT was as follows: complete reponsee (CR) in six patients (12%), very good partial response (VGPR) in 15 (29%), partial response (PR) in 16 (31%), stable disease (SD) in eight (16%), relapse/progression in three (6%), and three patients were not treated prior to ASCT (6%).

Transplant characteristics, engraftment and consolidation/maintenance

Melphalan conditioning dose (available in 47 patients, 92%)

Table 1. Characteristics of the study population at diagnosis and at transplantation (N=51).

Characteristics at diagnosis	Values
Male sex, N (%)	32 (63)
Underlying plasma cell disorder, missing N=14, 27%, N (%)	
Myeloma	23 (62)
Smoldering myeloma	3 (8)
MGUS	11 (30)
RRT-dependant, missing N=11, 22%, N (%)	
Yes	21(53)
No	19 (47)
Lytic bone lesions, missing N=13, 25%, N (%)	
No	32 (84)
Minor	4 (11)
Major	2 (5)
Bone marrow plasmacytosis %, missing N=11, 22%, median (IQR)	10 (7.8-20)
Patients with bone marrow plasmocytosis ≥10%, N (%)	23 (45)
Patients with bone marrow plasmocytosis ≥60%, N (%)	1 (2)
Monoclonal protein isotype, missing N=7, 14%, N (%)	
IgG	11(25)
IgA	1 (2.5)
Light chain	31 (70)
Ig D	1 (2.5)
International Staging System, missing N=38, 75%, N (%)	
I	1(7)
II	4 (31)
III	8 (62)
Serum light chain mg/L	
κ, missing N=16, 31%, median (IQR)	575 (146-1,095)
λ, missing N=17, 33%, median (IQR)	20 (12-44)
Involved/uninvolved FLC ratio, missing N=17, 33%, median (IQR)	21 (2.9-83.3)
FLC ratio >100, missing N=17, 33%, N (%)	6 (18)
Serum creatinine μmol/L, missing N=10, 20%, median (IQR)	233 (159-467)
Proteinuria (mg/24 hours), missing N=21, 41%, median (IQR)	1,813 (445-5,974)
Characteristics at transplant	**Values**
Pretransplant induction, missing N=7, 14%, N (%)	
No therapy	2 (5)
Bortezomib-based therapy	39 (89)
Cyclophosphamide-based therapy	1 (2)
VAD	1 (2)
Dexamethasone alone	1 (2)
Age in years, median (IQR)	55 (49-61)
Serum creatinine μmol/L, missing N=11, 22%, median (IQR)	280 (146-510)
Proteinuria (mg/24 hours), missing N=31, 61%, median (IQR)	569 (178-1,961)
RRT dependant, missing N=12, 26%, N (%)	
Yes	17 (45)
No	22 (55)
Time in months from diagnosis to transplant, median (range)	7 (6-13)
Karnofsky score, missing N=9, 18%, N (%)	
> 80	33 (79)
≤ 80	9 (21)

IQR: interquartile range; MGUS: monoclonal gammopathy of unknown significance; RRT: renal replacement therapy; FLC: free light chain ratio, monoclonal protein isotype is defined by serologic immunofixation; VAD: vincristine adriamycine dexamethasone.

was 100 mg/m^2 in 11 patients (23%), 140 mg/m^2 in 26 patients (55%) and 200 mg/m^2 in ten patients (21%). In patients on RRT: the melphalan conditioning dose was 200 mg/m^2 in one, 140 mg/m^2 in nine and 100 mg/m^2 in seven, in patients not on RRT: 200 mg/m^2 in seven, 140 mg/m^2 in 11 and 100 mg/m^2 in three (for 9 patients: unknown whether or not they were on RRT).
Median number of CD34$^+$ cells x10^6/kg infused was 3.4 (IQR, 2.5-4.6) and 13 (33%) received GCSF post ASCT. The median time to neutrophil engraftment was 12 days (IQR, 11-13) and median time to platelet engraftment was 13 days (IQR, 11-16). Out of a total of 39 patients (76%) with data available, five patients (13%) had received post-ASCT consolidation. Consolidation comprised bortezomib-based regimens (N=4) or pomalidomide plus dexamethasone plus daratumumab (N=1). Three patients (8%) had maintenance treatment post-ASCT out of a total of 37 with data available (73%).

Hematological response at day +100 post-autologous stem cell transplantation

The best hematological response at day +100 post-ASCT (available in 39 patients, 76%) was as follows: CR: 17 (43.6%), VGPR: nine (23.1%) and PR: ten (33.3%) and three patients who had progressed at day +100 (missing 12 [23.5%]). Response improvement from pre-ASCT to day +100 post-ASCT is shown in Table 2.

Renal outcome

From the time of LCDD diagnosis to ASCT, among the 51 patients, 33 patients were assessable (11 patients did not have data on RRT status, 6 patients were not assessable because the eGFR at diagnosis was >50 mL/min and in 1 case the eGFR was missing at diagnosis). Among these 33 assessable patients: 21 patients were on dialysis at some point from diagnosis, one patient reached a partial renal response (PRenal), one patient a minimal renal response (MRenal), one patient progressed and nine patients had no response. Concerning patients on dialysis: 21 patients were on dialysis at some time point between diagnosis and ASCT (11 unknown), 17 at time of ASCT and 16 after ASCT (1 patient went off dialysis 14 months after ASCT). These numbers do not take into account patients who proceeded to renal transplantation. There was no change in RRT status at day +100 in either the 17 RRT-dependent or 21 independent patients. Figure 1A shows eGFR at ASCT, and at +3, +6 and +12 months among 37 patients with known RRT status and eGFR data available. In patients with measurements at both time points, the mean eGFR improved slightly within the first 3 months post-ASCT in patients not on RRT at ASCT with the mean eGFR increasing from 52 at ASCT to 57 mL/min/1.73 m^2 (paired t test, P=0.19). The eGFR evolution for each individual patient is shown in Figure 1B as well as the mean eGFR between ASCT and 1 year post-ASCT for patients not on RRT as estimated using the linear mixed effects model including 126 eGFR measurements obtained from 37 patients. Estimated mean eGFR at ASCT was 50.7 mL/min/1.73m^2 (95% CI: 39.4-62.1) in those not on RRT. There was no significant changes in eGFR after ASCT (test whether slope is different from 0; P=0.64,). Altogether, three of 27 evaluable patients (11%) improved their renal function according to IMWG criteria (Table 3). Of 40 patients with data available on renal transplantation status, the cumulative incidence of renal transplantation at 4 years after ASCT was 27% (95% CI: 13-41). Renal transplantations were performed between 6.3 and 52.9 months post-ASCT with a median of 24.7 months. One patient who was on RRT at the time of transplant got off dialysis 14 months after the transplant (without renal transplantation).

Survival, relapse incidence and non-relapse mortality

Median follow-up time after ASCT was 84 months (IQR, 46-122). Outcomes after ASCT are shown in Figure 2 for all patients. The 100-day and the 2-year cumulative incidence of NRM was 2% (95% CI: 0-6). At 6 years post-ASCT, OS was 88% (95% CI: 78-98) and PFS was 44% (95% CI: 28-60). Median OS was not reached (NR), median PFS was 65 months (95% CI: 45-103; IQR, 27.9-NR) and 2-year cumulative RI was 17% (95% CI: 6-27). Nine patients died during the follow-up: six (67%) of relapse/progression, two (22%) infection and one (11%) organ damage/failure. The only patient who died before relapse/progression had multiple organ failure (including renal) at day 9.
In univariable analyses, RRT status at ASCT was not signifi-

Table 2. Hematological responses between autologous stem cell transplantation and day 100 following autologous stem cell transplantation in 39 patients.

Response, N (%)	Total number of assessable patients N=39
Worsening	3 (7.7)
VGPR-PR	3 (7.7)
Stability	15 (38.5)
CR-CR	5 (12.8)
VGPR-VGPR	3 (7.7)
PR-PR	7 (18.0)
Improvement	21 (53.8)
Not treated - VGPR	1 (2.6)
Relapse - PR	2 (5.1)
Relapse - VGPR	1 (2.6)
SD - PR	1 (2.6)
SD - CR	2 (5.1)
PR - VGPR	4 (10.2)
PR - CR	4 (10.2)
VGPR - CR	6 (15.4)

For 12 (23%) of the total 51 patients no day 100 response data was available, hence only the data of 39 patients is shown. Percentages shown are calculated as the percentage of all patients with an evaluable response at day 100. Responses were assessed according to criteria for response to treatment in immunoglobulin light chain amyloidosis.[14] CR: complete response; VGPR: very good partial response; PR: partial response; SD: stable disease.

cantly associated with OS and PFS (*Online Supplementary Figure S1*). Undergoing ASCT in or after the year 2012 was associated (log-rank *P*=0.05) with a better OS (6-year OS: 100% *vs.* 75%), women (log-rank *P*=0.05) tended towards a better OS (6-year OS: 100% *vs.* 82%). Karnofsky performance status, age and status of disease at ASCT (VGPR or better *vs.* other) did not have a significant association with any outcome measure in this small cohort.

Status post autologous stem cell transplanatation

Figure 3 shows the probability of being in different stages of renal and hematological disease post-ASCT for patients on RRT (Figure 3A) and patients not on RRT at ASCT (Figure 3B). All patients started as being event-free, and could subsequently move to either having had a hematological relapse or progression, having had a renal transplantation, a combination of these two events or death. At 4 years post-ASCT the probability for a patient on dialysis at ASCT to be event-free was 24% (95% CI: 11-54), to have had a renal transplantation (possibly after of followed by hematological relapse) was 58% (95% CI: 39-85), to be in a state of hematological relapse was 22% (95% CI: 10-52) and to have died was 6% (95% CI: 1-27). For patients who were not on RRT at ASCT these 4-year estimates were 54% (95% CI: 37-78), 11% (95% CI: 3-43), 35% (95% CI: 17-73) and 4% (95% CI: 0-37) respectively.

Discussion

This is the first international, multicenter, retrospective study analyzing outcomes following ASCT in patients with LCDD. Even though a significant proportion (45%) of the patients were on RRT at the time of transplant, we observed a low 2-year cumulative NRM rate of only 2% for such a high-risk population. Moreover, hematological responses by day +100 post-ASCT were very encouraging accompanied by more modest improvements in renal function. Indeed, no patient of the non RRT group had worse renal function after ASCT and 11 % improved their renal function at day 100.

Table 3. Renal responses at day 100 post autologous stem cell transplantation in 38 patients with renal replacement therapy status at autologous stem cell transplantation available.

Renal response at day 100 post-ASCT	N (%)*
Total number of patients	38
Total number of assessable patients	27 (100)
CRenal	1 (4)
PRenal	0
MRenal	2 (7)
No response	7 (26)
Progression	0
Still on dialysis	17 (63)
Not assessable (baseline eGFR ≥50 mL/min/1.73 m^2)	8
Not assessable (missing baseline or day 100 eGFR)	3

Responses were assessed according to the International Myeloma Working Group Recommendations for the diagnosis and management of myeloma-related renal impairment.[16] CRenal: complete renal response; PRenal: partial renal response; MRenal: minimal renal response. ASCT: autologous stem cell transplantation; eGFR: estimated glomerular filtration rate. The response reported are based on improvement from pre-transplant until day 100 post-transplant. *Percentages calculated for the total number of assessable patients.

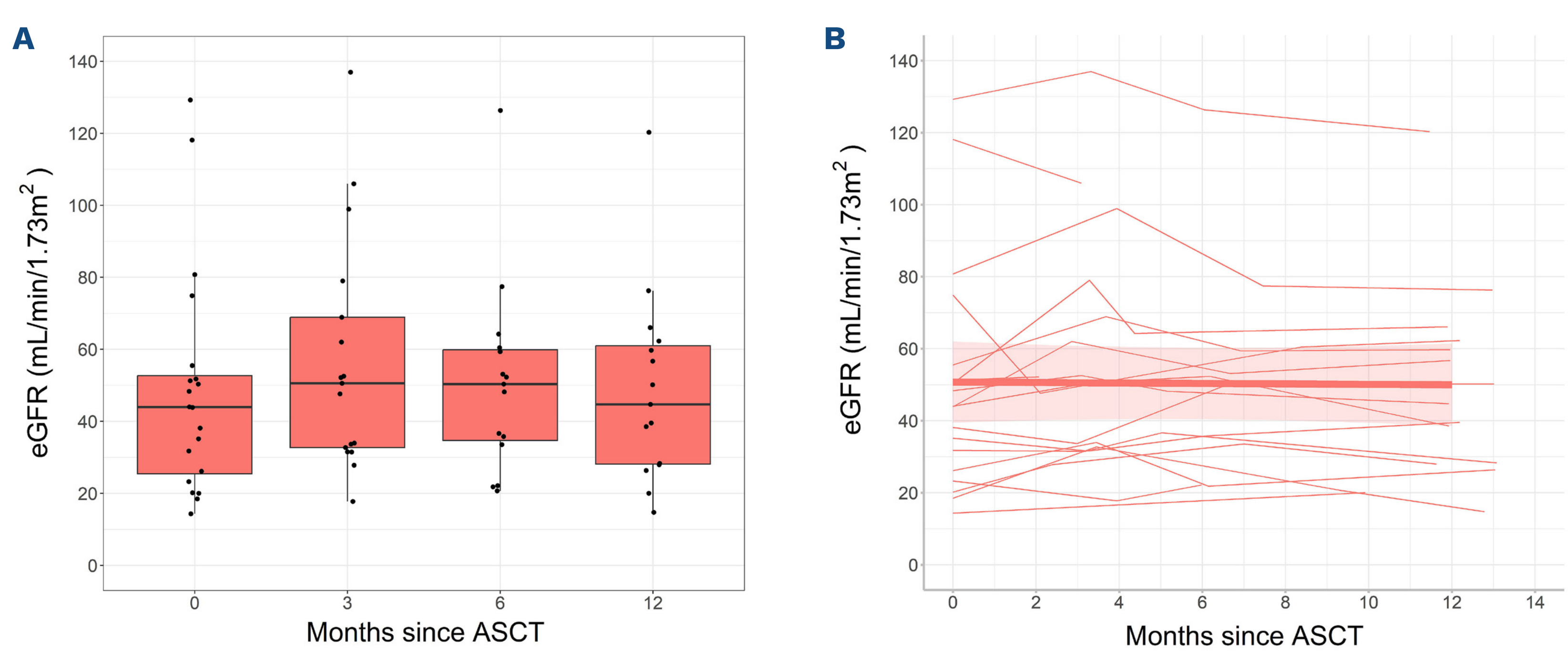

Figure 1. Estimated glomerular filtration rate at autologous stem cell transplantation, and 3, 6 and 12 months post-autologous stem cell transplantation in renal replacement therapy-independent patients. (A) Data shown as boxplots. The horizontal line shows the median, edges of the box show the interquartile range (IQR) and end of the whiskers show 1.5xIQR. (B) Individual estimated glomerular filtration rate (eGFR) trajectories in renal replacement therapy-independent patients, the estimated mean eGFR and 95% confidence interval around the mean estimated using a linear mixed effects model. ASCT: autologous stem cell transplantation.

Our experience is in keeping with prior reports, albeit of much smaller cohorts, that have described an important role for ASCT in patients with monoclonal immunoglobulin deposition disease (MIDD). Weichman and colleagues described six patients, five with LCDD and one with light chain crystal deposition disease (LCCDD), who underwent ASCT and who achieved a good outcome with acceptable toxicity.[20] Hassoun *et al.* described that most patients in a small cohort (N=7) demonstrated complete hematologic remission (CHR) followed by renal improvement and reversal of RRT dependence in one case.[21] Royer and colleagues subsequently reported their experience in 11 patients with LCDD/HCDD who received a variety of therapeutic regimens.[10] Regarding ASCT response, they too reported an overall favorable outcome, including CHR in five patients, improvement of renal function in four patients and several patients with cardiac and/or hepatic involvement who additionally demonstrated organ-specific improvements. Lorenz and co-workers reported the long-term outcome after ASCT of six patients. Although one patient did not survive the procedure, five had a hematological response by standard criteria and four who were not on RRT at the time of transplantation had a renal response as assessed by improvements in their GFR.[12] More recently, a single-center reported their experience with 36 patients, 32 AL amyloidosis and four with MIDD, all on RRT. Here, the NRM at day +100 post-ASCT was 8%, at 1 year 70% achieved a CHR and the median OS for the entire cohort was 5.8 years.[13]

We observed an initial increase in renal function by day +100 post-ASCT which was not statistically significant for

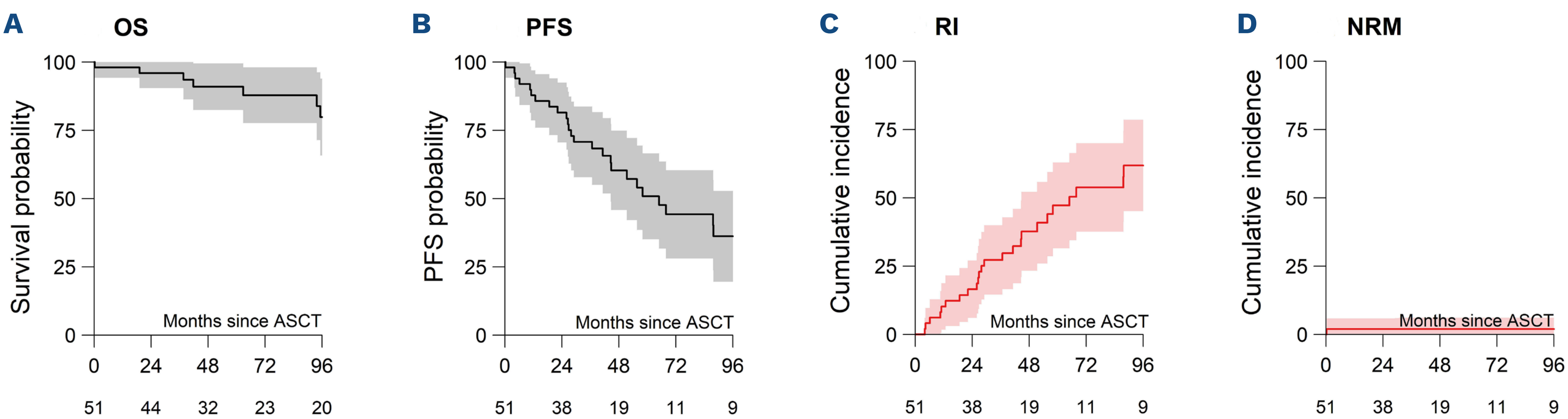

Figure 2. Survival, relapse incidence and non-relapse mortality. Probability of (A) overall survival (OS), (B) progression-free survival (PFS), (C) cumulative incidence of relapse (RI) and (D) non-relapse mortality (NRM). Numbers below the graphs show the number at risk. Shaded areas show the 95% confidence intervals.

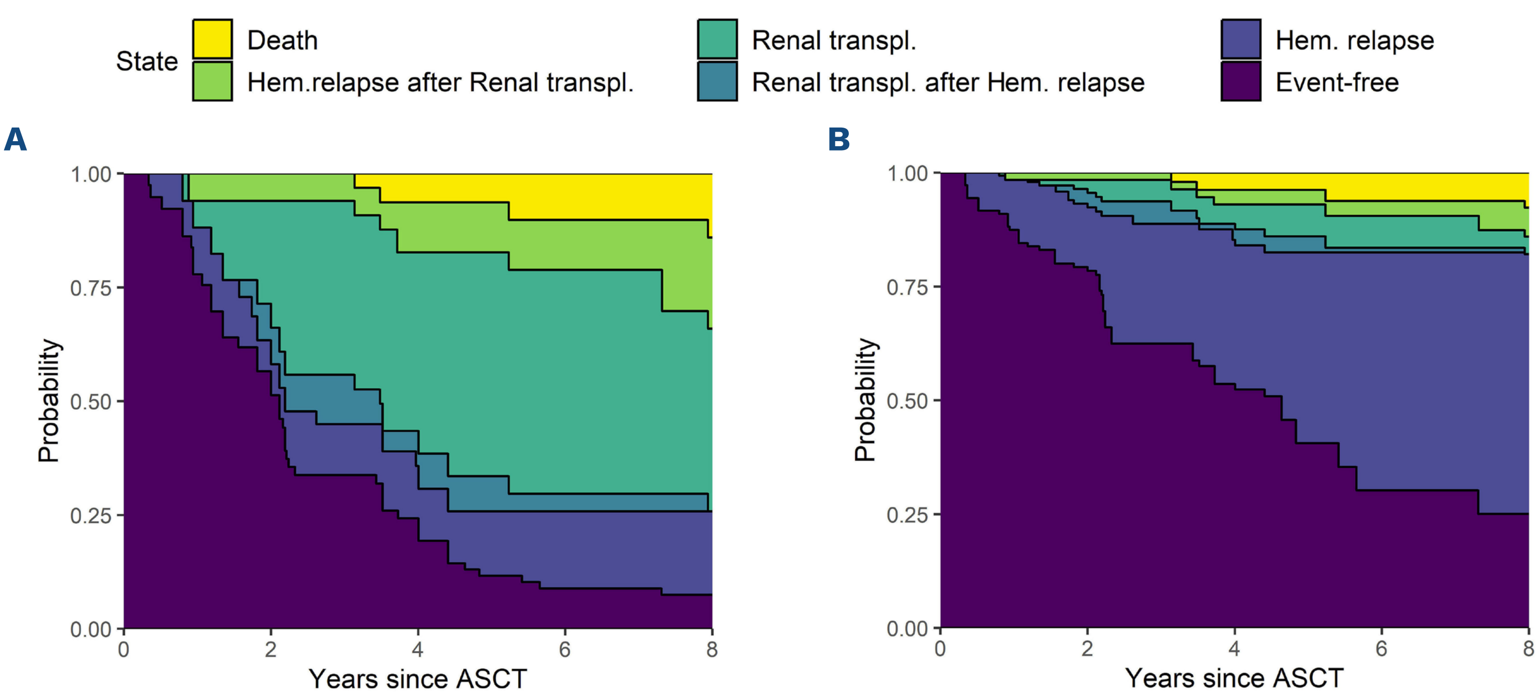

Figure 3. Probability of being in different stages of (combinations of) hematological and renal disease after autologous stem cell transplantation in patients, based on a multi-state model. (A) Patients on renal replacement therapy (RRT) and (B) patients not on RRT. At each time point the distance between two adjacent curves represents the probability of being in the corresponding state. The probability of being 'event-free' decreases over time and the probability of being in intermediate states 'renal transplantation', 'hematological relapse', 'hematological relapse after renal transplantation' and 'hematological relapse followed by renal transplantation' can both increase and decrease over time, whereas the probability of 'death' can only increase over time. Hem: hematological; transpl.: transplantation.

improvement. The success of ASCT in curbing continued renal dysfunction may clearly depend on achieving CHR. Indeed, in similar other monoclonal gammopathy of renal significance, it was possible to correlate the renal response with the hematologic response. Recently, a large French study, based on 255 MIDD patients, identified several factors associated with renal response, such as achievement of at least a very good partial hematological response, and the absence of severe interstitial fibrosis on diagnostic kidney biopsy.[22] Deep hematologic response was also associated with OS. In order to further improve the renal function, one should therefore attempt to deepen the hematological response. Therefore, in this setting, maintenance treatment post-ASCT may potentially be beneficial as has been clearly shown post transplantation in myeloma patients with normal renal function.[23]

Historically, long-term renal recovery after ASCT was not possible for patients with LCDD; however, with the advent of new myeloma-directed treatments and deeper hematological responses, some patients can now become RRT independent. In our study, even though there was no long-term renal improvement, because the hematological disease was under control, many patients could subsequently undergo successful renal transplantation although it is important to stress that renal transplantation was performed because the hematological disease was under control.

There are some limitations to this study. We analyzed renal function only according to the International Myeloma Working Group criteria and we now know that it may not be optimal: amyloid renal response criteria are also valuable and the two assessments are complementary especially for patients who do not have a low eGFR at diagnosis and those without proteinuria.[24] There is also a selection bias in that only LCDD patients deemed as being sufficiently fit would be considered for and offered the ASCT option, with many requiring renal support during the procedure. Moving forwards, the relevance of the ASCT option in the context of a progressively expanding, therapeutic armamentarium is a consideration. Even though our data shows encouraging results, novel immunotherapeutics can significantly improve overall outcomes in plasma cell disorders. For example, targeted therapeutic monoclonal antibodies have shown great promise in both AL amyloidosis and LCDD.[25] In the latest series of eight patients with LCDD and MM treated with the anti-CD38 monoclonal antibody daratumumab because of hematologic relapse, a hematologic response was obtained in seven of eight patients, with stabilization of renal function.[26] Other immunotherapies such as T-cell engagers[27] and chimeric antigen receptor T cells,[28] alone or in combinations, have rapidly entered the clinical arena and in preliminary experiences, they seem to be administered safely to patients with renal insufficiency.[29] However, ASCT still represents a highly effective (and cost-effective) means of inducing complete serological responses, which are important in protecting against further renal damage from LCDD, in both 'original' and transplanted kidneys. The combined use of ASCT alongside modern targeted therapeutics enhance the probabilities of achieving and prolonging complete serological responses through maintenance and salvage therapies. This will not only enhance PFS and OSl, but also reduces the risk of renal progression, which is associated with therapeutic and prognostic disadvantages especially for those requiring RRT. Moreover, a deep sustained complete serological response enhances consideration and delivery of renal transplantation in appropriately selected patients. Patients should be considered at an early stage to factor in appropriate planning and maximize the long term benefits of renal transplantation.[30,31]

In summary, we report a multicenter experience with the use of ASCT in patients with LCDD, an experience that corroborates previous reports highlighting significant benefits. Renal dysfunction including RRT dependence can be reversed or stabilized with ASCT, with or without subsequent renal transplantation. Because in this setting, the hematological disease is under control for a long period of time, renal transplantation can be a valid option. Ultimately, the goal of successful therapy may hinge on the complete suppression of light chain production. Further benefit in patients achieving less than a CR after a single ASCT may be provided by the use of novel agents and post-transplant maintenance therapy.

Disclosures

No conflicts of interest to disclose.

Contributions

LGa, LGr, SS, PH, DMcL designed the study. RM, LV, GK, KK, DD, MK, JK, HO, MJPC, JP, AR, US, JAS, CTH, XL, LG, JDS, KR and MB enrolled patients. LGa, LGr, Lde W, JAS, SS, PH and DMcL analyzed the data. LGa, LGr, Lde W, JAS, SS, PH and DMcL wrote the manuscript.

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Data-sharing statement

Data can be obtained upon request to the corresponding author.

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