

Improved Outcomes After Autologous Hematopoietic Cell Transplantation for Light Chain Amyloidosis: A Center for International Blood and Marrow Transplant Research Study

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A B S T R A C T

Purpose

Autologous hematopoietic cell transplantation, or autotransplantation, is effective in light-chain amyloidosis (AL), but it is associated with a high risk of early mortality (EM). In a multicenter randomized comparison against oral chemotherapy, autotransplantation was associated with 24% EM. We analyzed trends in outcomes after autologous hematopoietic cell transplantation for AL in North America.

Patients and Methods

Between 1995 and 2012, 1,536 patients with AL who underwent autotransplantation at 134 centers were identified in the Center for International Blood and Marrow Transplant Research database. EM and overall survival (OS) were analyzed in three time cohorts: 1995 to 2000 (n = 140), 2001 to 2006 (n = 596), and 2007 to 2012 (n = 800). Hematologic and renal responses and factors associated with EM, relapse and/or progression, progression-free survival and OS were analyzed in more recent subgroups from 2001 to 2006 (n = 197) and from 2007 to 2012 (n = 157).

Results

Mortality at 30 and 100 days progressively declined over successive time periods from 11% and 20%, respectively, in 1995 to 2000 to 5% and 11%, respectively, in 2001 to 2006, and to 3% and 5%, respectively, in 2007 to 2012. Correspondingly, 5-year OS improved from 55% in 1995 to 2000 to 61% in 2001 to 2006 and to 77% in 2007 to 2012. Hematologic response to transplantation improved in the latest cohort. Renal response rate was 32%. Centers performing more than four AL transplantations per year had superior survival outcomes. In the multivariable analysis, cardiac AL was associated with high EM and inferior progression-free survival and OS. Autotransplantation in 2007 to 2012 and use of higher dosages of melphalan were associated with a lowered relapse risk. A Karnofsky score less than 80 and creatinine levels 2 mg/m² or greater were associated with worsened OS.

Conclusion

Post-transplantation survival in AL has improved, with a dramatic reduction in early post-transplantation mortality and excellent 5-year survival. The risk-benefit ratio for autotransplantation has changed, and randomized comparison with nontransplantation approaches is again warranted.

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INTRODUCTION

Light-chain amyloidosis (AL) is a multisystemic disease caused by a malignant plasma cell clone with resultant insoluble fibrillar deposition.¹ Amyloid fibrils derived from misfolded immunoglobulin light chains cause direct organ toxicity leading to organ failure and death. Current AL therapies focus on eliminating the source of amyloid, that is, the plasma cell clone, by using chemotherapy. However, che-

motherapy has minimal effect on preformed organ amyloid; consequently, organ improvements lag behind hematologic responses.² After diagnosis, patients, particularly those with advanced cardiac AL, are at increased risk for early death from progressive heart failure and sudden death despite the use of effective chemotherapy.³

The role of autologous hematopoietic cell transplantation, or autotransplantation, in AL is controversial. Single-center studies revealed good

outcomes in terms of hematologic responses and organ improvement.⁴⁻⁶ However, the prospective randomized clinical trial reported in 2007 in which autotransplantation was compared with oral melphalan and dexamethasone showed inferior survival with autotransplantation.⁷ Inferior outcomes were related to high early mortality (EM) of 24% in the transplantation arm and were partly attributed to the inclusion of patients with severe cardiac amyloidosis⁷ and possibly related to low-volume amyloid transplantation centers.⁸ Since that study,⁷ use of cardiac biomarkers—serum troponin T and *N*-terminal of brain natriuretic peptide—has helped improve detection and risk stratification in patients with cardiac AL.⁹ These refined selection criteria for autotransplantation, along with improvements in supportive care of patients in the peritransplantation period, have translated into a decrease in the post-transplantation EM to less than 5% at large amyloid centers in the United States.^{10,11} We hypothesized that outcomes of autotransplantation among patients with AL have improved over time. In addition, we wanted to test the utility of autotransplantation in AL in practice and to assess if center AL transplantation experience affects outcomes. We undertook a retrospective study using the Center for International Blood and Marrow Transplant Research (CIBMTR) database to address these issues.

PATIENTS AND METHODS

Data Source

The CIBMTR is a prospectively maintained registry that collects transplantation data from over 320 centers worldwide. Data are collected at two levels: registration and research. The registration data include disease type, age, sex, date of diagnosis, graft type, conditioning regimen, post-transplantation disease progression, survival, and cause of death, and it includes all transplantations reported to the CIBMTR. More-detailed clinical data are collected from a subgroup of registered patients selected for research data by using a weighted randomization scheme. Both the registration data and the research data are collected pretransplantation, at 100 days and 6 months post-transplantation, and annually thereafter until death or last follow-up.

Patients

Included in this study were patients registered with the CIBMTR in North America between 1995 and 2012 for an autotransplantation for AL within 24 months of diagnosis. Data from these patients were analyzed in three arbitrarily grouped cohorts based on the year of transplantation: 1995 to 2000, 2001 to 2006, and 2007 to 2012. Registration data set was used to assess survival outcomes. Robust research data were available for a subgroup of 354 patients who underwent transplantation between 2001 and 2012. This subgroup was analyzed for hematologic and organ responses and in multivariable analyses. Key characteristics and survival were compared between the registration set and this subset to confirm that the subgroup was a random representative of the data set (Appendix Table A1, online only, and Appendix Table A2, online only). Data accuracy was established by means of physician review (by A. D'Souza and P.H.) of discrepant data when present, and centers were contacted if needed for additional review.

Definitions of Early Mortality, Response, and Center Effect

EM was defined as mortality from any cause after transplantation within the defined time windows of 30 and 100 days. This differed from transplantation-related mortality (TRM), which excluded patients who died as a result of progressive AL or relapse. This avoided attribution bias wherein mortality from organ amyloid in the post-transplantation period could have

been labeled as being caused by disease and, thus, causing an underestimation of TRM. Use of EM ensured that the risk of post-transplantation death was not underreported and that mortality in the post-transplantation period was accurately described irrespective of attribution to disease versus treatment-related causes.

The uniform system proposed at the 10th International Symposium on Amyloidosis was used to define hematologic and renal response and progressions.¹² In 2012, new criteria were proposed to define hematologic response and progression on the basis of free light-chain (FLC) analysis.³ Because FLC and cardiac biomarkers were collected only after 2008, we were unable to apply the 2012 hematologic or cardiac response criteria to our data set retrospectively. Among organ responses, only renal response is reported in this analysis.

The association between amyloid transplantation volume and survival was analyzed as center experience.⁸ Owing to a wide variability in the numbers of transplantations performed by centers over the 18-year period of this study, center effect was calculated by using the mean number of amyloid transplantations performed per year over the 4 years¹³ between 2009 and 2012. Center experience in transplantation for AL was considered a dichotomous variable. After we performed maximum likelihood testing using the various cut points of two, three, four, five, and 10 amyloid transplantations per year, we established that a minimum of four AL transplantations per year was an informative divider for this analysis.

Statistical Analysis

Patient-, disease- and treatment-related factors were compared by using the [CHI]² test for categorical variables and the Kruskal-Wallis test for continuous variables. Outcomes analyzed included EM, relapse and/or progression, progression-free survival (PFS), and overall survival (OS). Estimates of outcomes were reported as probabilities with 95% CIs. The probability of OS was calculated with the Kaplan-Meier estimator, with the variance estimated by using the Greenwood formula. Survival curves were compared with the log-rank test. Multivariable analysis was performed by using the research data subset ($n = 354$) with a Cox proportional hazards model in which the transplantation period cohort of 2001 to 2006 versus 2007 to 2012 was the main effect. Other factors included age at transplantation, race, pretransplantation Karnofsky performance score (KPS), hematopoietic cell transplantation-comorbidity index (HCT-CI), serum creatinine level, serum albumin level, bone marrow plasma cell burden, amyloid organ pattern, number of involved organs, pretransplantation chemotherapy, time from diagnosis to transplantation, melphalan dose in mg/m² and center effect. The assumption of proportional hazards was tested for each variable, and factors violating the proportionality assumption were adjusted by stratification. Potential interactions between the main effect and all other significant risk factors were tested. All *P* values were two-sided, and $P < 0.05$ was considered to indicate a significant difference.

RESULTS

Patient-, Disease-, and Transplantation-Related Variables

Table 1 displays available characteristics for the entire group from 1995 to 2012 ($n = 1,536$), and Table 2 shows data for the subset with detailed level data from 2001 to 2012 ($n = 354$). The median age at transplantation was 56 years, with evidence of increasing age at transplantation with successive time cohorts (Table 1). Most patients underwent transplantation within 6 months of diagnosis. The underlying plasma cell clone was λ in 72% of cases (Table 2). The M-spike was nonquantifiable in 42% of patients; when quantified, the median size was 0.6 g/dL. The distribution of cardiac and renal involvement was similar between the groups. Few patients had noncardiac, nonrenal organ involvement in this

Table 1. Characteristics of Patients Who Underwent First AutoHCT for AL and Reported to CIBMTR

Characteristic	No. (%)			
	Year of Transplantation			Overall (N = 1,536)
	1995-2000 (n = 140)	2001-2006 (n = 596)	2007-2012 (n = 800)	
No. of centers	50	93	104	134
Age at transplantation, years				
Median age (range)	54 (31-71)	57 (23-78)	59 (26-77)	56 (23-78)
18-39	12 (9)	21 (4)	23 (3)	272 (18)
40-49	30 (21)	123 (21)	119 (15)	604 (39)
50-59	65 (46)	244 (41)	295 (37)	362 (24)
60-65	30 (21)	118 (20)	214 (27)	242 (16)
≥ 66	3 (2)	90 (15)	149 (19)	56 (4)
Male sex	85 (61)	355 (60)	483 (60)	923 (60)
Karnofsky score < 80	21 (15)	82 (14)	110 (14)	213 (14)
Time from diagnosis to transplant, months				
< 6	80 (57)	399 (67)	483 (60)	962 (63)
6-12	41 (29)	145 (24)	214 (27)	400 (26)
12-24	19 (14)	52 (9)	103 (13)	174 (11)
Median follow-up of survivors from diagnosis (range), months	146 (7-209)	97 (5-152)	33 (6-94)	56 (5-209)
Median follow-up of survivors from transplantation (range), months	142 (4-194)	93 (3-145)	25 (3-76)	49 (3-194)

Abbreviations: AL, light-chain amyloidosis; autoHCT, autologous hematopoietic cell transplantation; CIBMTR, Center for International Blood and Marrow Transplant Research.

cohort, and renal involvement without cardiac involvement was the most frequently observed pattern. We found no difference in the 2001-to-2006 and 2007-to-2012 groups in terms of the number of organs involved, and four or more organ were involved in 12% and 11% patients, respectively. Most patients had no treatment before transplantation, but more patients received treatment in 2007 to 2012 than in 2001 to 2006 (33% v 13%, $P < .001$). Melphalan dosage was reduced most frequently in 2007 to 2012, with 64% of patients receiving less than 180 mg/m² of melphalan conditioning, and 34% received less than 140 mg/m².

EM and Causes of Death in 1,536 Patients

Figure 1A shows EM for the three groups. Mortality at 30 and 100 days declined from 11% (95% CI, 7% to 17%) and 20% (95% CI, 14% to 27%), respectively, for the 1995-to-2000 group to 5% (95% CI, 4% to 7%) and 11% (95% CI, 8% to 13%) for the 2001-to-2006 group to 3% (95% CI, 2% to 4%) and 5% (95% CI, 4% to 7%) for the 2007-to-2012 group ($P < .001$). No difference was seen in EM based on the time from diagnosis to transplantation. Rates were, at less than 6 months, 12% (95% CI, 8% to 17%); at 6 to 12 months, 5 (95% CI, 1% to 11%); and 12 to 24 months, 8% (95% CI, 2% to 18%). Causes of death reported within the first 100 days were attributed to amyloid and organ failure in most patients (83%), followed by infection (8%), nonengraftment (3%), and unknown causes (6%).

OS in 1,536 Patients

Median follow-up was 56 months (5 to 209 months) from the time of diagnosis. One-, 3- and 5-year OS in successive cohorts improved from 75% (95% CI, 65% to 82%), 64% (95% CI, 56% to 72%), and 55% (95% CI, 46% to 63%), respectively, for 1995 to 2000 to 85% (95% CI, 81% to 87%), 72% (95% CI, 68% to 75%), and 61% (95% CI, 57% to 65%), respectively, for 2001 to 2006 and to 90% (95% CI,

88% to 92%), 83% (95% CI, 80% to 86%), and 77% (95% CI, 72 to 82%), respectively, for 2007 to 2012 ($P < .001$; Fig 1B).

We observed no difference in OS based on the time from diagnosis to transplantation. Rates were, at less than 6 months, 73% (95% CI, 67% to 79%); at 6 to 12 months, 81% (95% CI, 71% to 89%); and at 12 to 24 months, 81% (95% CI, 61% to 92%; $P = 0.22$).

For patients with cardiac amyloidosis, 3-year OS improved from 62% (95% CI, 48% to 75%) in 2001 to 2006 to 67% (95% CI, 52% to 80%) in 2007 to 2012 ($P = .59$; Fig 2A). For those with renal and without cardiac amyloidosis, 3-year OS improved from 78% (95% CI, 68% to 86%) in 2001 to 2006 to 89% (95% CI, 82% to 95%) in 2007 to 2012 ($P = .03$; Fig 2B).

Response Rates in the Subset of 354 Patients

A best hematologic response to transplantation was available in 89% and 97% of patients in the 2001-to-2006 and 2007-to-2012 groups, respectively. A renal response at any point after autotransplantation was available in 70% and 78% of patients in 2001 to 2006 and 2007 to 2012, respectively. Table 3 shows a breakdown of hematologic and renal responses that were observed in this cohort. The hematologic response rate was higher in the 2007-to-2012 cohort than in the 2001-to-2006 cohort.

Center Effects in the Subset of 354 Patients

EM was worse among 81 centers that performed fewer than four AL transplantations per year, that is, low volume, than in others. Their mortality rate of 5% (95% CI, 3% to 7%) at 30 days and 7% (95% CI, 5% to 10%) at 100 days compared with 1% (95% CI, 0.4% to 3%) at 30 days and 3% (95% CI 2% to 6%) at 100 days for centers that performed four or more AL transplantations a year, or high volume ($n = 11$; $P = .01$; Fig 2C). No statistically significant difference was found for age, KPS, HCT-CI, cardiac amyloidosis, number of organs

Table 2. Baseline Characteristics of Patients From 2001-2012 Subgroup

Characteristic	No. (%)		P
	Year of Transplantation		
	2001-2006 (n = 197)	2007-2012 (n = 157)	
No. of centers	51	41	
Age at transplantation, years			.05
Median age (range)	57 (31-75)	58 (26-74)	.28
18-39	3 (2)	8 (5)	
40-49	43 (22)	19 (12)	
50-59	79 (40)	67 (43)	
60-65	36 (18)	36 (23)	
≥ 66	36 (18)	27 (17)	
Male sex	116 (59)	100 (64)	.36
Race			.12
White	169 (86)	134 (85)	
African American	17 (9)	13 (8)	
Other/unknown	11 (6)	10 (6)	
Karnofsky score < 80	31 (16)	20 (13)	.38
HCT comorbidity score			< .001
0	36 (18)	33 (21)	
1-2	74 (38)	46 (29)	
≥ 3	19 (10)	63 (40)	
Unknown*	68 (35)	15 (10)	
	Disease Related		
Involved serum free light chain (after year 2008)			NE
No. evaluated	NE	110	
λ	—	79 (72)	
κ	—	31 (28)	
Serum monoclonal immunoglobulin at diagnosis, g/dL			
No. evaluated	74	98	
Nonquantifiable	25 (34)	48 (49)	
Median when measured (range)	0.7 (0.0002-5.0)	0.5 (0.0004-6.3)	.28
Bone marrow plasma cells, %			.53
≤ 10	136 (69)	114 (73)	
> 10	26 (13)	22 (14)	
Unknown	35 (18)	21 (13)	
Serum creatinine at any time pretransplantation, mg/dL			.06
< 2	158 (80)	118 (75)	
≥ 2	39 (2)	35 (22)	
Unknown	0	4 (3)	
Serum albumin at any time before pretransplantation, g/dL			.003
< 2.5	74 (38)	49 (31)	
2.5-3	37 (19)	27 (17)	
≥ 3	72 (37)	80 (51)	
Unknown	14 (7)	1 (< 1)	
	Organ Involvement		
Organ or system			
Cardiac	75 (38)	59 (38)	.47
Renal	142 (72)	120 (76)	.01
Hepatic	20 (10)	9 (6)	.56
Autonomic nervous system	27 (14)	13 (8)	.11
No. of organs involved			.37
1	55 (28)	52 (33)	
2	60 (30)	51 (32)	
3	48 (24)	33 (21)	
≥ 4	23 (12)	18 (11)	
Unknown	11 (6)	3 (2)	
Type of organ involvement			.28
Cardiac (cardiac ± renal ± others)	75 (38)	59 (38)	
Predominant renal (renal ± others)	85 (43)	77 (49)	
Other	26 (13)	18 (11)	
Unknown	11 (6)	3 (2)	

(continued on following page)

Autologous Transplantation in AL amyloidosis

Table 2. Baseline Characteristics of Patients From the 2001-to-2012 Subgroup (continued)

Characteristic	No. (%)		P
	Year of Transplantation		
	2001-2006 (n = 197)	2007-2012 (n = 157)	
	Transplantation Related		
CD34 cells infused, × 10 ⁶ /kg	160	113	.01
Median (range)	4.8 (1.0-16.8)	4.0 (1.2-17.3)	
Melphalan dose, mg/m ²			.01
Median (range)	175 (86-241)	143 (86-219)	.15
<140	65 (33)	69 (44)	
140-180	31 (16)	31 (20)	
≥ 180	86 (44)	54 (34)	
Missing/outliers	15 (8)	3 (2)	
Pretransplantation chemotherapy			< .001
Untreated	167 (85)	105 (67)	
Melphalan based	13 (7)	15 (10)	
IMiD based	12 (6)	22 (14)	
Bortezomib based	0	15 (10)	
Missing	5 (3)	0	
Time from diagnosis to transplantation, months			.92
< 6	131 (66)	103 (66)	
6-12	46 (23)	36 (23)	
12-24	20 (10)	18 (11)	
Median follow-up of survivors from diagnosis (range), months	89 (5-51)	56 (12-82)	
Median follow-up of survivors from transplant (range), months	77 (3-145)	49 (7-75)	

Abbreviations: HCT, hematopoietic cell transplantation; IMiD, immunomodulatory drug; NE, nonevaluable.
*HCT comorbidity index was not collected before 2007.

involved with amyloidosis, melphalan conditioning dosage, or pre-transplantation chemotherapy between the high-volume and low-volume centers (Appendix Table A3, online only). Both high- and low-volume centers showed an improvement in reported EM in the three time cohorts ($P < .01$; Fig 2D).

Multivariable Analysis in the Subset of 354 Patients

Table 4 shows results of the multivariable analysis. Adjusted analysis showed no difference between the 2001-to-2006 cohort and the 2007-to-2012 cohort for EM, PFS, or OS. The analysis for relapse and/or progression was nonproportional, and the optimal cut point

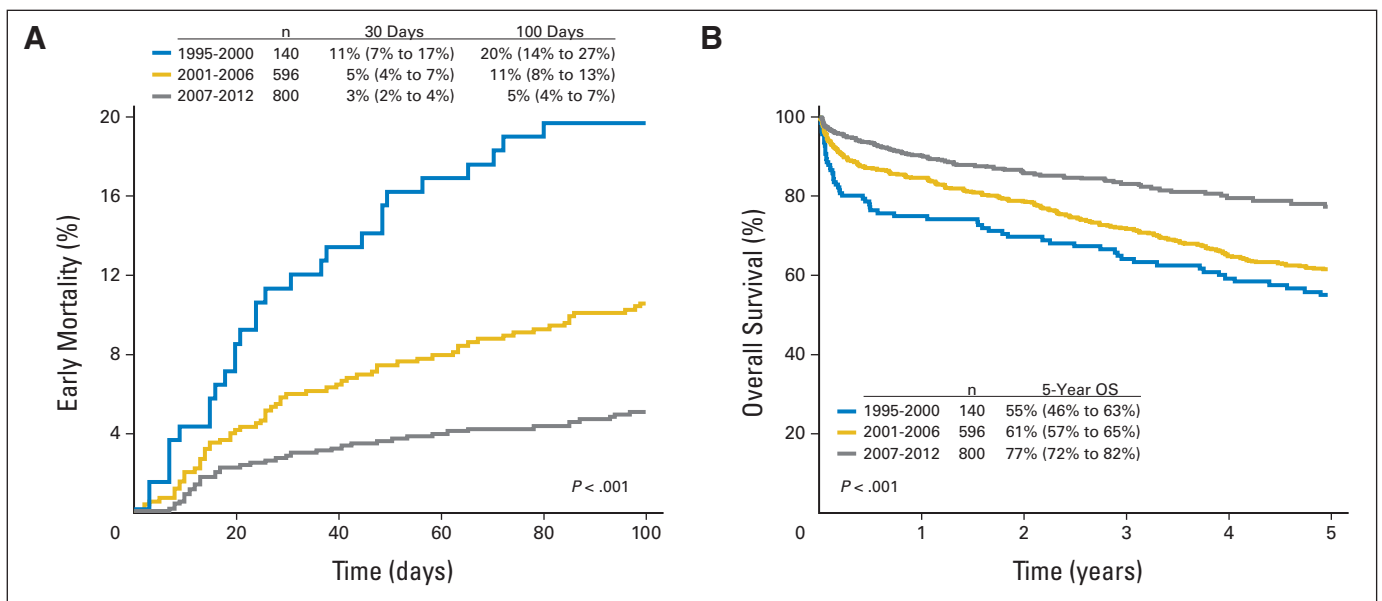


Fig 1. Probabilities of (A) early mortality and (B) overall survival (OS) in light-chain amyloidosis after transplantation for all three time cohorts.

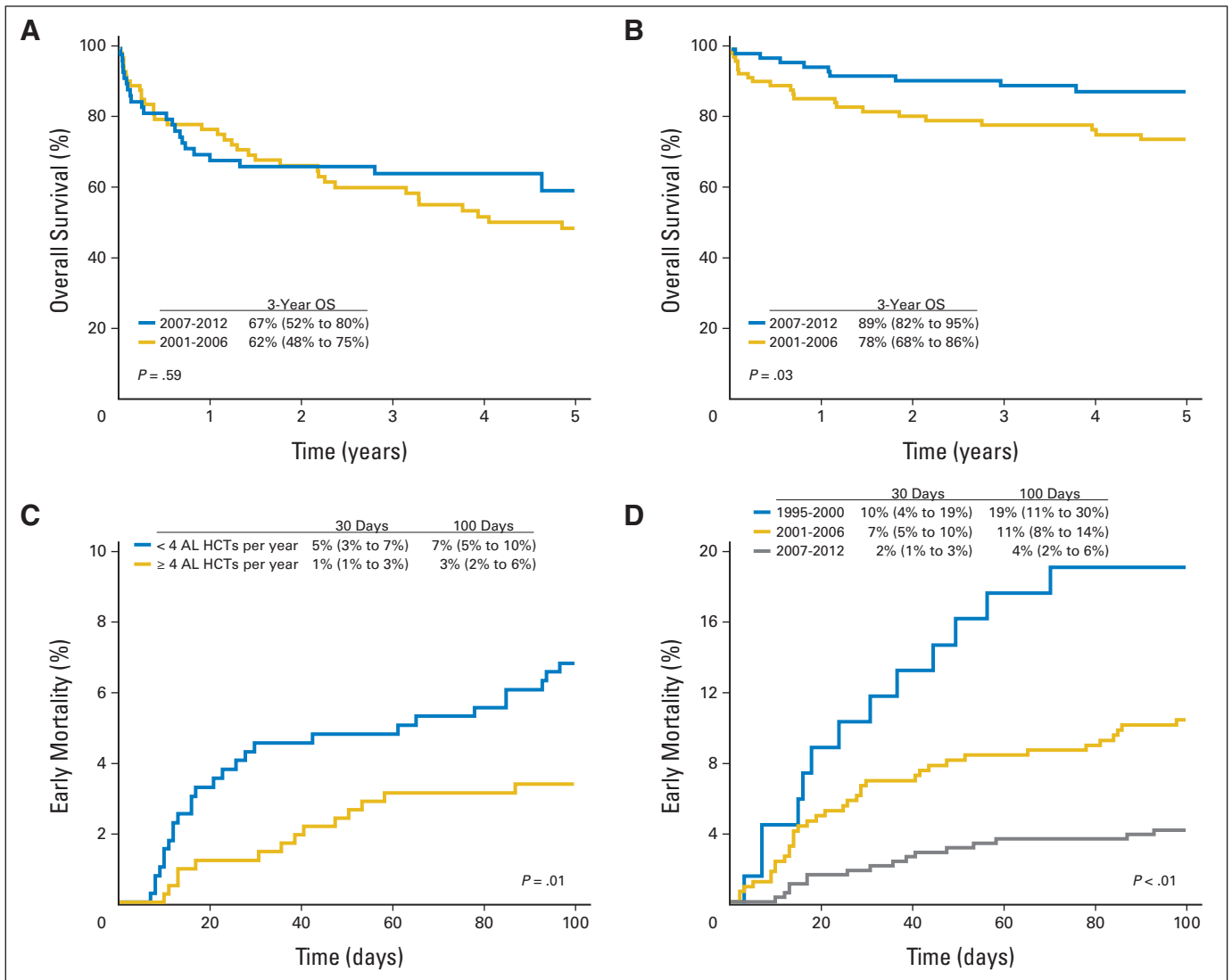


Fig 2. Trends in (A) overall survival (OS) for cardiac light-chain amyloidosis (AL); (B) OS for renal, noncardiac AL; (C) early mortality (EM) based on center experience; and (D) time trends in improvement in EM among centers.

identified was 9 months after transplantation. During the initial period, no difference occurred between the 2001-to-2006 and 2007-to-2012 cohorts for relapse and/or progression. After 9 months, the relapse and/or progression rate was lower in the 2007-to-2012 cohort. The presence of cardiac involvement was associated with increased EM (hazard ratio [HR], 3.5; 95% CI, 2 to 6.4; $P < .001$), worse PFS (HR, 2.0; 95% CI, 1.7 to 3.0; $P < .001$), and OS (HR, 2.5; 95% CI, 1.6 to 3.9; $P < .001$).

DISCUSSION

We describe outcomes after autotransplantation in the largest cohort of patients with AL reported to date. We make a number of clinically important observations. First, impressive reduction in EM has been achieved in recent years, and this is superior to the reported TRM of 24% from the only randomized clinical trial we know of in this setting.⁷ Second, cardiac amyloid involvement remains the critical vari-

able associated with worse outcomes, with no improvement in outcomes of patients with cardiac amyloidosis over time. Third, center experience with AL transplantation is important in reducing EM. Centers that perform four or more AL transplantations per year report better results than those that do not. Fourth, 5-year survival in this real-world experience of autotransplantation has improved to 77% in the most recent cohort. This is comparable to data from specialized single centers and superior to the transplant arm of the randomized trial.^{7,14}

Although established as an effective treatment modality in AL, autotransplantation has been controversial, owing to inferior outcomes reported in the prospective, randomized controlled, phase III trial described in 2007.⁷ Further, more recently, combination chemotherapy using novel agents such as bortezomib with alkylators has been shown to be associated with prompt and deep hematologic responses in the upfront setting.¹⁵⁻¹⁸ Therefore, the role of autotransplantation in AL has been further questioned. This is reflected in our

Table 3. Hematologic and Renal Responses Observed With Transplantation

Response	2001-2006 (n = 197)		2007-2012 (n = 157)		P
	No.	%	No.	%	
Best hematologic response					.005
Complete response	60	30	58	37	
Partial response	44	22	53	34	
Stable disease	42	21	25	16	
Progression	7	4	3	2	
Nonevaluable*	22	11	14	9	
Missing	22	11	4	3	
Best renal response					.30
Response	61	31	51	32	
Stable disease	48	24	47	30	
Progression	7	4	10	6	
Nonevaluable*	22	11	14	9	
Missing	59	30	35	22	

*Nonevaluable was noted for patients who died in the first 100 days after transplantation.

study; the number of transplantations performed in the US did not rise as rapidly after 2007 as they did in the preceding years.

Despite similar proportion of patients with cardiac involvement, transplantation after 2007 was associated with lower EM and superior OS than the earlier time periods. Therefore, EM improvements appeared to be multifactorial, representing improvements in supportive care and a higher level of experience overall in caring for these patients with complex conditions and not merely selection of fitter patients. Among patients with a renal, noncardiac pattern of AL involvement, outcomes improved significantly over time. However, for patients with cardiac AL, we were unable to demonstrate a statistically significant change in survival over time. A similar finding has been reported by others with novel chemotherapies^{17,19,20} and highlights the importance of earlier diagnosis of AL disease and an unmet need for safer and more effective therapies for patients with advanced cardiac amyloidosis, including antifibril therapies.

In our subset analyses of 354 patients, we were able to study response rates and prognostic factors. The response rate at day 100 was limited by missing data, particularly for the 2001-to-2006 group; therefore, it is not shown. However, when we assessed best hematologic response to transplantation, we noted more complete and partial hematologic responses in 2007 to 2012 than in 2001 to 2006. More patients received pretransplantation induction chemotherapy during 2007 to 2012, but melphalan conditioning doses were also lower in this period than in others. Of interest, renal response rates were equivalent in 2001 to 2006 and 2007 to 2012 at 31% and 32%, respectively; this result is similar to renal response of 33% reported after chemotherapy.²¹ However, fewer patients, less than 10%, in both groups had progression of renal AL. This was much lower compared with renal progression after chemotherapy, even among the 50% of patients who have complete and partial hematologic responses.²¹

A number of pretransplantation factors have been shown to be prognostic after autotransplantation for AL. Cardiac biomarkers using serum cardiac troponin T and N-terminal of brain natriuretic peptide provide a simple clinical prognostication system of staging AL amyloidosis,⁹ improving our ability to screen for patients with advanced cardiac amyloidosis who are at increased risk for post-

Table 4. Multivariable Analysis of Outcomes

Effect	No.	Hazard Ratio	95% CI	P
Early mortality	336			
2001-2006	183	1.0		
2007-2012	153	0.956	0.567 to 1.613	.87
Type of organ involvement				< .001
Cardiac	128	1.000		
Renal, noncardiac	152	0.285	0.156 to 0.518	< .001
Other	42	0.268	0.096 to 0.752	.01
Missing	14	0.206	0.028 to 1.507	.12
Relapse and or progression	331*			
Early event, 0-9 months				.02
2001-2006	178	1.000		
2007-2012	153	1.440	0.561 to 3.700	.45
Late event, > 9 months				
2001-2006	145	1.000		
2007-2012	119	0.321	0.137 to 0.753	.01
Pretransplantation chemotherapy				
Untreated	259			
Treated	72	0.545	0.239 to 1.245	.15
Melphalan dose, mg/m ²				.001
< 140	128	1.000		
140-180	58	0.511	0.235 to 1.114	.09
≥ 180	131	0.237	0.118 to 0.474	< .001
Missing	14	0.487	0.116 to 2.049	.33
Progression-free survival	336			
2001-2006	183	1.000		
2007-2012	153	0.821	0.553 to 1.219	.33
Karnofsky score				.001
≥ 80	265	1.000		
< 80	49	2.41	1.556 to 3.749	< .001
Missing	22	1.305	0.560 to 3.040	.54
Type of organ involvement				.003
Cardiac	128	1.000		
Renal, noncardiac	152	0.504	0.331 to 0.766	.001
Other	42	0.424	0.217 to 0.832	.013
Missing	14	0.531	0.189 to 1.492	.23
Overall survival	350†			
2001-2006	197	1.000		
2007-2012	153	0.703	0.460 to 1.075	.1
Karnofsky score				.001
≥ 80	278	1.000		
< 80	51	2.670	1.694 to 4.206	< .001
Missing	21	1.644	0.696 to 3.882	.26
Pretransplantation serum creatinine level, mg/dL				.02
< 2	276	1.000		
≥ 2	74	1.7000	1.072 to 2.697	.02
Type of organ involvement				.001
Cardiac	131	1.000		
Renal, noncardiac	161	0.402	0.255 to 0.632	< .001
Other	44	0.444	0.218 to 0.905	.03
Missing	41	0.425	0.129 to 1.401	.16

*Five patients were excluded because pretransplantation chemotherapy data were not available.
†Four patients excluded because pretransplantation serum creatinine levels were not available.

transplantation complications and EM. Other known risk factors associated with transplantation mortality include performance status and multiorgan involvement with amyloidosis.^{22,23} In addition, lowered melphalan conditioning intensity to adjust for risk has been

associated with a reduced response rate.²⁴ In this study, we confirm that cardiac involvement, poor renal function, poor KPS less than 80, and use of melphalan conditioning less than 180 mg/m² are associated with worse outcomes. The HCT-CI is a transplantation-specific prognostic variable that was described and validated in the mid-2000s. Although we were able to calculate it many patients using reported comorbidities, this variable was unavailable in the pre-2008 patient set. A bone marrow plasma cell clone greater than 10% has been found to be associated with worse outcomes,^{25,26} but this finding was not replicated in our study. Although pretransplantation chemotherapy was not associated with improved outcomes, most of the pretransplantation chemotherapy included nonbortezomib-based approaches.

In addition to the superior hematologic responses noted previously, patients in the 2007-to-2012 cohort also had a lower risk of relapse starting 9 months after transplantation. This was an interesting finding because lower doses of melphalan conditioning, which was more common in the 2007-to-2012 period than in others, was an independent predictor of relapse. Post-transplantation consolidation with bortezomib has been associated with deepening of response rates.²⁷ In our analysis, only 38 patients received any post-transplantation consolidation, and further analyses could not be performed because of low numbers.

The best results for autotransplantation in AL have been reported from specialized, high-volume centers in contrast to the multicenter, randomized trial experience. It has been proposed that center experience in treating patients with AL is important, with low-volume centers having higher EM rates.⁸ Indeed, in our cohort, transplantation centers performing fewer than four AL transplantations per year had higher EM rates than those of centers performing four or more transplantations. Lack of differences in the patient, organ, or chemotherapy-related factors between high- and low-volume centers led us to believe that high-volume centers do not necessarily select fitter patients for transplantation. Rather, they may be more experienced in supporting and treating these patients in the early post-transplantation period. However, owing to the small numbers in the subset analysis, our analysis was not powered to show significant differences in outcomes on the basis of center volume in the multivariable analysis after other factors were adjusted.

Our study had a number of limitations inherent to its retrospective nature and the long interval under study. Amyloidosis manage-

ment is a dynamic field, and, during study inclusion, criteria for response and organ involvement changed twice.^{12,28} Variability in reporting by centers and the introduction of markers such as FLC, cardiac biomarkers, and HCT-CI at various points during this period were other issues inherent to the interval under study. Data regarding FLC and cardiac biomarkers were not collected in our database after 2008, but serial FLC or cardiac biomarkers were reported for too few patients to adequately define amyloid stage²⁹ or response by using the 2012 criteria described by Palladini et al.²⁸ Another limitation of our study was our inability to stratify the severity of cardiac involvement because cardiac biomarker information was not uniformly reported. Therefore, although percentages of patients reported with cardiac involvement were similar between the 2001-to-2006 and 2007-to-2012 periods, we do not know if cardiac stage was similar between these cohorts. Finally, our data were limited to individuals undergoing transplantation, who are inherently a selected group of better-risk patients.³⁰

Although our study does not replace a controlled, transplantation-versus-nontransplantation trial, it is reassuring to see that excellent outcomes of autotransplantation previously reported from large single centers were replicated in practice capturing most AL transplantations in the US. With the availability of novel plasma cell-directed agents such as bortezomib, we propose that it is time to reconsider a multi-institutional study to compare transplantation, perhaps limited to high-volume centers, versus novel nontransplantation therapy.

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Disclosures provided by the authors are available with this article at www.jco.org.

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Improved Outcomes After Autologous Hematopoietic Cell Transplantation for Light Chain Amyloidosis: A Center for International Blood and Marrow Transplant Research Study

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Appendix

Variable	Research Data Set (n = 354)	Entire Cohort (N = 1,356)	P
Age at transplantation, years			
Median age (range)	57 (26-75)	58 (23-78)	.40
18-39	11 (3)	44 (3)	
40-49	62 (18)	242 (17)	
50-59	146 (41)	539 (39)	
60-65	72 (20)	332 (24)	
≥ 66	63 (18)	239 (17)	
Sex			.73
Male	216 (61)	838 (60)	
Female	138 (39)	558 (40)	
Country			.08
United States	329 (93)	1,330 (95)	
Canada	25 (7)	66 (5)	
Race			.88
White	303 (86)	1,188 (85)	
African American	30 (8)	112 (8)	
Others	12 (3)	49 (4)	
Missing	9 (3)	47 (3)	
Karnofsky score*			.02
80-100	278 (79)	1,031 (74)	
< 80	51 (14)	192 (14)	
Missing	25 (7)	173 (12)	
Time from diagnosis to transplantation, months			.56
< 6	234 (66)	882 (63)	
6-12	82 (23)	359 (26)	
12-24	38 (11)	155 (11)	
Median follow-up of survivors (range), months	61 (3-145)	47 (3-145)	

*P for nonmissing groups = .93.

Outcome	Research Data Set (n = 354)		Entire Cohort (N = 1,396)	
	Probability (%)	95% CI	Probability (%)	95% CI
Early mortality				
1 month	94	91 to 96	96	95 to 97
100 day	90	86 to 93	93	91 to 94
Overall survival, years				
1	83	79 to 87	88	86 to 89
3	76	71 to 80	77	75 to 80
5	70	64 to 75	68	65 to 71

NOTE. Log rank test P = .94.

Table A3. Comparison of Key Variables Between High- and Low-Volume Light-Chain Amyloidosis Transplantation Centers

Variable	Center Experience, No. of Transplantations				P
	< 4 (n = 91)		≥ 4 (n = 66)		
	No.	%	No.	%	
Age at transplantation, years					.60
18-39	3	3	5	8	
40-49	13	14	6	9	
50-59	40	44	27	41	
60-65	19	21	17	26	
≥ 66	16	18	11	17	
Karnofsky score					.68
80-100	71	78	52	79	
< 80	13	14	7	11	
Missing	7	8	7	11	
Time from diagnosis to transplantation, months					.49
< 6	63	69	40	61	
6-12	18	20	18	27	
12-24	10	11	8	12	
Cardiac involvement					.24
Yes	37	41	22	33	
No	32	35	32	48	
Missing	22	24	12	18	
Renal involvement					.65
Yes	68	75	52	79	
No	11	12	5	8	
Missing	12	13	9	14	
Organ involvement					.13
0	1	1	2	3	
1	29	32	23	35	
2	36	40	15	23	
3	18	20	15	23	
4	7	8	11	17	
Hematopoietic cell transplantation-comorbidity index					.15
0	25	27	8	12	
1	10	11	9	14	
2	13	14	14	21	
3	13	14	7	11	
4	24	26	19	29	
Missing	6	7	9	14	
Melphalan dose, mg/m ²					.20
< 140	35	38	34	52	
140-180	18	20	13	20	
> 180	37	41	17	26	
Missing	1	1	2	3	
Chemotherapy					.09
No chemotherapy	65	71	40	61	
Melphalan based	6	7	9	14	
Thalidomide based	2	2	7	11	
Lenalidomide based	9	10	4	6	
Bortezomib based	9	10	6	9	

NOTE. Center experience was measured by the mean number of light-chain transplantations performed at centers between 2009 and 2012. High volume was four or more transplantations per year, and low volume was four or fewer transplantations per year.