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Outcomes of Patients with Light Chain Amyloidosis Who Had Autologous Stem Cell Transplantation with 3 or More Organs Involved

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A B S T R A C T

Prior reports have suggested that 3 or more organs involved is a contraindication for autologous stem cell transplant (ASCT) in amyloid light chain (AL) amyloidosis. Therefore, most centers limit transplantation to patients who have no more than 2 organs significantly involved. We retrospectively reviewed all patients with AL amyloidosis with ≥3 involved organs and who had ASCT between 1996 and 2015 at Mayo Clinic, Rochester, Minnesota to assess transplant safety and outcomes. Seventy-five patients with ≥3 organs involved underwent ASCT. Median age at diagnosis was 54 years, and 67% were men. The heart was involved in 95%, followed by the kidneys (84%). Thirty-eight patients (51%) had no induction treatment before ASCT. Full-dose melphalan (200 mg/m^2) was given in 45%, and the remainder received 140 mg/m^2. Overall hematologic response rate was 75%. The median progression-free survival (PFS) and overall survival (OS) were 16 and 68 months, respectively. The 100-day mortality was 16%, and 44 patients (59%) died during follow-up. The most common causes of death were cardiovascular events (32%) and progressive amyloidosis (25%). On multivariable analysis, predictors for PFS were Mayo 2012 stage III/IV (relative risk [RR], 3.3; $P = .0012$) and hematologic response (at least very good partial response; RR, .4; $P = .012$). An N-terminal pro–brain natriuretic peptide (NT-proBNP) level of ≥2000 pg/mL was an independent predictor for shorter PFS (RR, 2.6; $P = .013$). Predictors for OS included any hematologic response (RR, .12; $P = .0015$), melphalan 200 mg/m^2 (RR, .2; $P = .014$), and Mayo 2012 stage III/IV (RR, 7.7; $P = .0002$). An NT-proBNP level ≥ 2000 pg/mL was a powerful predictor of OS (RR, 4; $P = .013$). The number of organs involved (3 versus >3) did not significantly impact PFS or OS. We conclude that the high prevalence and severity of cardiac involvement are the main drivers for the poor outcome in patients who have ≥3 organs involved. Using selection criteria defined for safe transplantation in cardiac amyloidosis should result in low therapy-related mortality independent of the number of organs involved. The severity of cardiac involvement should be the major criterion for transplanting patients with AL amyloidosis that have ≥3 organs involved and not merely the number of organs involved.

INTRODUCTION

Amyloid light chain (AL) amyloidosis can affect multiple organs. Making a decision about treating with autologous stem cell transplantation (ASCT) is challenging. As we recognize and risk stratify the disease better, we are now being more selective in choosing patients for ASCT. Previously, performance status, kidney function, and alkaline phosphatase were used to assess eligibility for ASCT in patients with AL amyloidosis [1]. In 2008 Gertz et al. [2] concluded that troponin T was a predictor of short-term survival after ASCT, because patients with troponin T levels of .06 μg/L or higher had a day 100 all-cause mortality rate of 28%, compared with 7% for patients with levels lower than .06 μg/L. They concluded that a troponin T level < .06 μg/L was required to be eligible for ASCT. Cardiac involvement is 1 of the main limiting factors for ASCT in AL amyloidosis [3].

Having more than 2 organs involved has been considered high risk for ASCT in some studies [4–7]. In addition, some suggest that having more than 2 major organs involved is considered a contraindication for ASCT [8,9]. However, the definition of organ involvement differs between studies, and the extent of amyloid organ involvement varies significantly. Insurance companies, not infrequently, reject a request for ASCT in patients with AL amyloidosis because more than 2

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organs are involved, based on these publications. To understand this better, we looked at our patients who had AL amyloidosis involving ≥3 organs and who had ASCT between 1996 and 2015 at Mayo Clinic, Rochester, Minnesota to assess safety and outcomes.

METHODS

We retrospectively identified patients who had AL amyloidosis with ≥3 organs involved and who had ASCT between March 1996 and January 2016 at the Mayo Clinic, Rochester, Minnesota. The study was approved by the Mayo Clinic Institutional Review Board. The diagnosis of AL was confirmed with biopsy, and the definition of organ involvement was according to consensus criteria [10]. Organ involvement included heart, liver, kidney, gastrointestinal, lung, nerve (including peripheral or autonomic neuropathy), and soft tissue (including tongue, skin, muscle, or carpal tunnel). Details about baseline characteristics, laboratory, imaging, and other required information were recorded. The revised Mayo 2012 staging system [11] was applied, if possible, because some patients were transplanted before the availability of light chains and/or cardiac biomarkers. The criteria for ASCT continue to be refined with time. Before 2008 we did not use the criteria of troponin T < .06 μg/L to exclude patients. Our patients were part of the cohort reported in a previous publication [12]. However, reporting specifically the outcome of patients who had AL amyloidosis with ≥3 organs involved post-ASCT was not an outcome assessed in that publication.

Currently, our selection criteria includes age 70 years or younger, systolic blood pressure ≥ 90 mm Hg, Eastern Cooperative Oncology Group performance score ≤ 2, high sensitivity cardiac troponin T < 75 ng/L, New York Heart Association functional class of I or II, and a creatinine clearance ≥ 30 mL/min, unless stable on dialysis. For all patients included in this analysis, the criterion of troponin T ≤ .06 μg/L was only implemented after 2008. Induction treatment was given before ASCT at physician discretion. Stem cell mobilization in general was performed using granulocyte colony-stimulating factor only. All patients received melphalan before their ASCT, and the decision regarding dose (200 mg/m^2 versus 140 mg/m^2) was left to the treating physician.

Response was assessed in all patients alive at day 100, according to published criteria [13]. Serum free light chain measurement was introduced in 2003, and patients before 2003 were not evaluated with the current response criteria. Complications post-ASCT were recorded, as well as mortality (both at 100 days and overall). One hundred day mortality was defined as any death from any cause during the 100 days post-ASCT. Progression-free survival (PFS) was defined as the time from ASCT to progression of disease, restarting therapy, or death. Overall survival (OS) was defined as the time from ASCT to death of any cause. Statistical analysis was done using JMP software (SAS Institute, Cary, NC), and survival analysis was done using the Kaplan-Meier method.

RESULTS

We identified 75 patients who had ≥3 organs involved. Their baseline characteristics are listed in Table 1. The median age at transplant was 54 years, and most patients were men (67%). Seventy-one patients (95%) had cardiac involvement. Other organs included kidneys (84%), liver (39%), nerve (including both autonomic and/or peripheral neuropathy, 39%), gastrointestinal (36%), and soft tissues (36%). Twenty patients (27%) required dialysis (hemodialysis or peritoneal), and 6 of these were on dialysis before ASCT. Fifty-six patients (75%) had 3 organs involved, 16 (21%) had 3 organs involved, and 3 patients (4%) had 5 organs involved. The λ light chain isotype was seen in 77% of patients. The number of transplants done annually has decreased over time, as safer therapies became available and improved screening of high-risk cardiac amyloidosis was implemented. Sixteen patients (21%) and 6 patients (8%) were transplanted after 2010 and 2013, respectively.

The median N-terminal pro–brain natriuretic peptide (NT-proBNP) and troponin T were 1903 pg/mL (interquartile range, 520-4707) and .02 μg/L (interquartile range, .1-.04), respectively. The median interventricular septal thickness was 15 mm, and the median ejection fraction was 63%. Thirty-eight patients (51%) had no previous induction treatment before their transplant, and the rest received steroids only (21%), melphalan (4%), immunomodulatory drugs (lenalidomide/thalidomide) (5%), bortezomib (15%), and other therapies (4%). According to the revised Mayo 2012 staging system [11], 11 patients (19%) had stage I, 19 (34%) had stage II, 20 (35%) had stage III, and 7 (12%) had stage IV disease. Mayo 2012 stage was not available in 18 patients. Conditioning with full-dose melphalan (200 mg/m^2) was used in 34 patients (45%) and the rest received a reduced dose (140 mg/m^2). In our institution ASCT is performed outpatient and patients are admitted only if clinically indicated. All patients required hospital admission, with a median of 7 days [2–17]. The timing of transplant, engraftment, and complications during the transplant are listed in Table 2.

Overall hematologic response was seen in 56 patients (75%), and 27 (36%) had complete response (CR) (Table 2). Seven patients could not be evaluated for response, because free light chains were not available. Twelve patients (16%) died during the first 100 days, and overall 44 (59%) died during the course

Table 1
Baseline Characteristics (N = 75)

Variable	Median (Interquartile Range)
Age, yr	54 (48-61)
Involved free light chain, mg/dL	18.5 (8.7-46)
Difference in free light chain, mg/dL	16.3 (8-43)
NT-proBNP before transplant, pg/mL	1903 (520-4707)
Troponin T, μg/L	.02 (.1-.04)
ALP, U/L	129 (86-250)
Albumin, g/dL	2.6 (2.1-3.2)
Creatinine, mg/dL	1.1 (.9-1.4)
Creatinine clearance, mL/min	69 (45-85)
24-hr urine protein, g	4 (1.5-7.6)
Variable	No. of Cases (%)
Male	50 (67)
Heart involvement	71 (95)
Kidney involvement	63 (84)
Required dialysis	20 (27)
Liver involvement	29 (39)
Gastrointestinal involvement	27 (36)
Neurologic involvement	29 (39)
Lung involvement	1 (1.3)
Soft tissue involvement	27 (36)
3 organs involved	56 (75)
4 organs involved	16 (21)
5 organs involved	3 (4)
Lambda light chain isotype	58 (77)
BMPCs ≥ 10	34 (45)
Prior treatment	
None	38 (51)
Corticosteroid only	16 (21)
Melphalan	3 (4)
IMiD-based	4 (5)
Bortezomib-based	11 (15)
Other	3 (4)
Mayo 2012 stage	
1	11 (19)
2	19 (34)
3	20 (35)
4	7 (12)

ALP indicates alkaline phosphatase; BMPCs, bone marrow plasma cells; IMiD, immunomodulatory drug.

Table 2
Transplant Variables and Outcomes (N = 75)

Variable	Value
Median number of apheresis collections (IQR)	2 (2-4)
Timing of transplant from diagnosis	
<6 mo	53 (71)
≥6 to ≤12 mo	15 (20)
> 12 mo	7 (9)
Conditioning	
Melphalan 200 mg/m^2	34 (45)
Melphalan <200 mg/m^2	41 (55)
Engraftment	
Median days to neutrophil engraftment (IQR)	14 (13-25)
Median days to platelet engraftment (IQR)	14 (12-17)
Median days in hospital (IQR)	7 (2-17)
Infection	30 (40)
Bleeding (gastrointestinal and other)	10 (13)
Mortality	
100 day	12 (16)
Overall	44 (59)
Cause of death	
Unknown	4 (9)
Infection	7 (16)
Cardiac	14 (32)
Progressive amyloidosis	11 (25)
Bleeding	5 (11)
Pulmonary embolus + bleeding	1 (2)
Acute leukemia	1 (2)
Ischemic stroke	1 (2)
Response	
CR	27 (36)
VGPR	16 (21)
Partial response	13 (17)
No response	19 (25)

Values are n (%) unless otherwise defined. IQR indicates interquartile range.

of the disease. Causes of death during the first 100 days included sepsis (25%), sudden cardiac death (25%), bleeding (33%), bleeding with a large pulmonary embolus (8%), and sepsis with heart failure (9%). Causes of death overall were cardiac (32%), progressive amyloidosis (25%), infections (16%), and bleeding (11%). The median PFS and OS were 16 and 68 months, respectively (Figure 1).

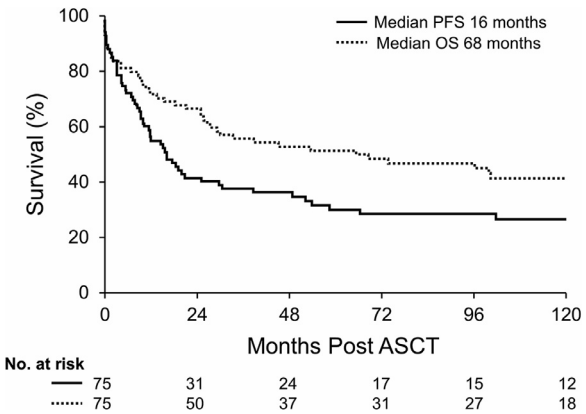

Figure 1. PFS and OS for all patients.

On univariable analysis, the NT-proBNP (≥2000 versus <2000), troponin T (≥.025 versus <.025), Mayo 2012 stage (III/IV versus I/II), and having at least very good partial response (VGPR) were statistically significant predictors of PFS (RR 3.6 [P < .0001], 1.9 [P = .02], 3.0 [P = .0008], and .34 [P = .0013], respectively). Two multivariable models were used for prediction of PFS: 1 that used Mayo 2012 stage (model 1) and 1 that looked at the variables of the stage separately (model 2). In model 1 Mayo 2012 stage and having at least VGPR were predictive, and in model 2 NT-proBNP level ≥ 2000 pg/mL and having at least VGPR were predictors of PFS (Table 3). The PFS for the Mayo 2012 stage (III/IV versus I/II) and response (≥VGPR versus <VGPR) are displayed in Figure 2. In Figure 3 the PFS for the NT-proBNP level ≥ 2000 is shown.

On univariable analysis, NT-proBNP (≥2000 versus <2000), troponin T (≥.025 versus <.025), Mayo 2012 stage (III/IV versus I/II), receiving melphalan at 200 mg/m^2, and having any hematologic response were statistically significant predictors of OS (RR 6.3 [P < .0001], 2.1 [P = .023], 5.7 [P < .0001], .5 [P = .02], and .2 [P = .0012], respectively). On multivariable analysis hematologic response, Mayo 2012 stage, and receiving melphalan 200 mg/m^2 were predictive for OS using model 1, whereas only NT-proBNP ≥ 2000 and hematologic response predicted OS using model 2 (Table 4). Figure 2 shows OS by Mayo 2012 stage and hematologic response. The OS for the NT-proBNP level is displayed in Figure 3. The number of organs involved (3 versus 4 to 5) was not significant for either PFS or OS.

DISCUSSION

The criteria for ASCT in AL amyloidosis continue to be updated. Previously, Gertz et al. [3] reported that the number of organs involved is critical for the decision to proceed to ASCT. More recently, however, the importance of cardiac biomarkers such as troponin T and NT-proBNP for evaluating patients for ASCT has been identified. Muchtar et al. [14] documented that with the new-generation high-sensitivity cardiac troponin T, also known as fifth-generation high-sensitivity cardiac troponin T assay, a cut-off value of 75 ng/L can be used to substitute the criterion of troponin T ≤ .06 μg/L. Sidiqi et al. [12] reported on the outcomes of 672 patients who had ASCT for their AL amyloidosis, and having more than 2 organs involved was not a predictor for OS. The number of organs involved "as a criteria" should be used with caution for multiple reasons. First, the amyloid involvement varies, and "minimal" versus "significant" involvement should be taken into consideration. Second, not all organs are the same, for example, having cardiac involvement is more significant than soft tissue involvement. Third, counting the number of organs varies between studies. For example, some consider autonomic neuropathy as a separate organ from peripheral nerve involvement. Finally, the poor outcome of patients who had more than 2 organs involved appears to be driven by cardiac involvement. Almost all our patients had cardiac involvement, and having NT-proBNP ≥ 2000 pg/mL was an independent predictor for shorter PFS and OS. Twelve patients (16%) died during the first 100 days, and of those 3 had a troponin T ≥ .06 μg/L. Overall, 44 patients (59%) died during the course of the disease, and 10 had a troponin T ≥ .06 μg/L. In total, 11 patients had troponin T levels ≥ .06 μg/L, and 10 (91%) died. These patients were all transplanted before the recommendations about troponin T came into effect in 2008. If these patients were not transplanted, the 100 day mortality would have been 12%. Most of our transplantations (nearly 80%) were done

Table 3
Multivariable Analysis for PFS

Multivariable Model 1			Multivariable Model 2		
Variable	RR (95% CI)	*P*	Variable	RR (95% CI)	*P*
Mayo 2012 stage (III/IV vs. I/II)	3.3 (1.6-6.7)	.0012	NT-proBNP (≥2000 vs. <2000)	2.6 (1.2-5.5)	.013
Hematologic response (≥VGPR vs. <VGPR), excluding 100 day TRM	.4 (.2-.8)	.012	Troponin (≥.025 vs. <.025)	1.6 (.7-3.3)	.23
			Hematologic response (≥VGPR vs. <VGPR), excluding TRM	.4 (.2-.8)	.016

CI indicates confidence interval; TRM, transplant-related mortality.

before 2010, reflecting the more careful assessment and selection of patients for safe transplantation with time.

Goodman et al. [4] reported the outcomes of patient who had ASCT for AL amyloidosis in the United Kingdom between 1994 and 2004; 92 patients underwent ASCT and 21 (23%) died during the first 100 days. Of patients who died during the first 100 days, 14 (67%) had 3 or more organs involved and 14 had cardiac involvement. It was not mentioned what percentage of patients who had ≥3 organs involved also had cardiac involvement, but given the predominance of cardiac involvement in the cohort, it was likely to be high. Overall, only 25 patients had ≥3 organs involved. Main predictors for transplant-related mortalities were the number of organ involved and performance status. The main predictors for OS in their study on multivariate analysis were cardiac, autonomic nerve, and liver involvement. Another study looked at the CR rates of 421 patients with AL amyloidosis who had ASCT [5]. In that study autonomic and peripheral neuropathy were considered 2 different organs, and 43% of all patients were considered to have ≥3 organs. In most studies and in the consensus [10], autonomic and peripheral neuropathy are considered as 1 organ. If considered as 1 organ, the results of the analysis that

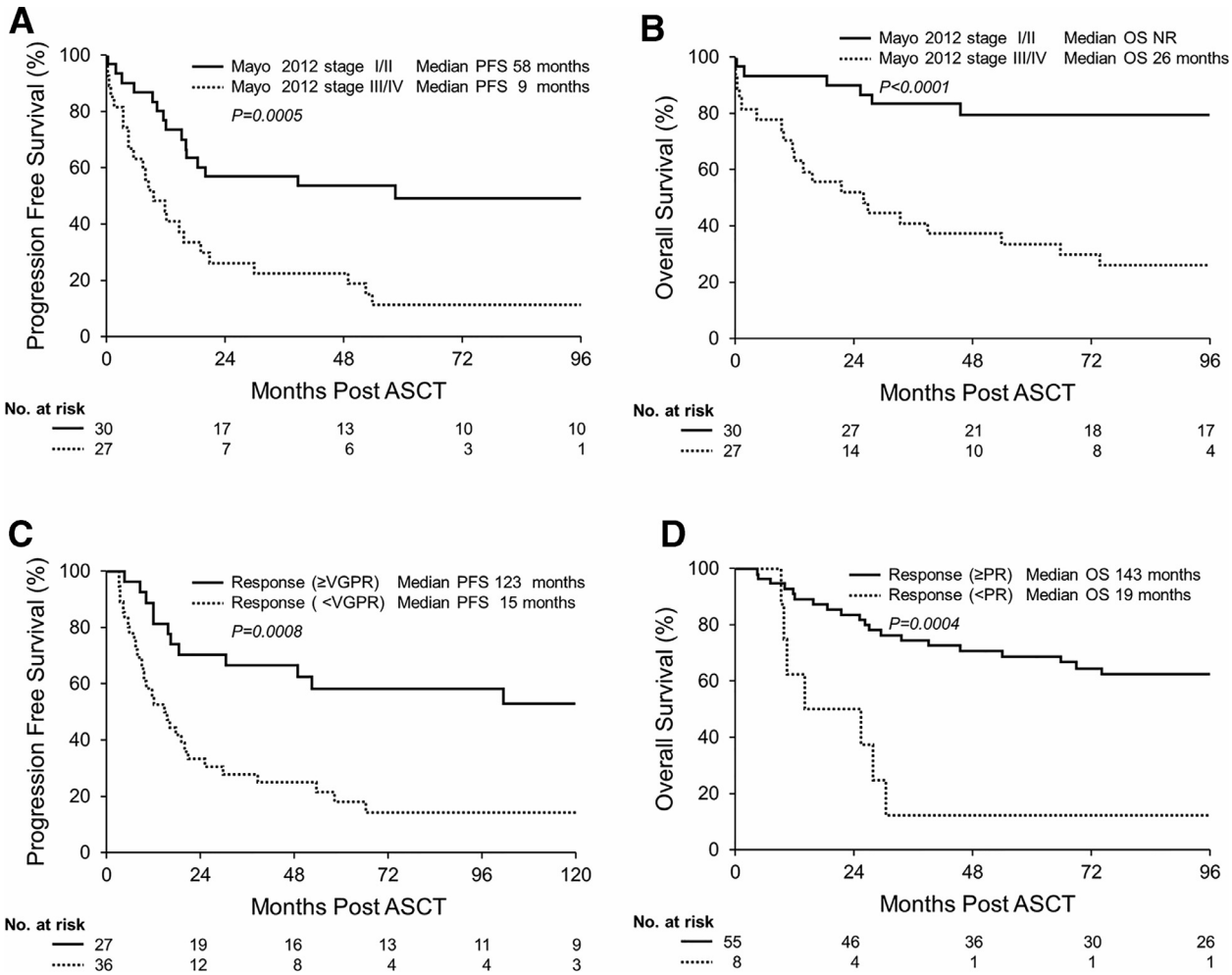

Figure 2. (A and B) PFS and OS according to the Mayo 2012 stage. (C and D) PFS and OS by response. PR indicates partial response; NR, not reached.

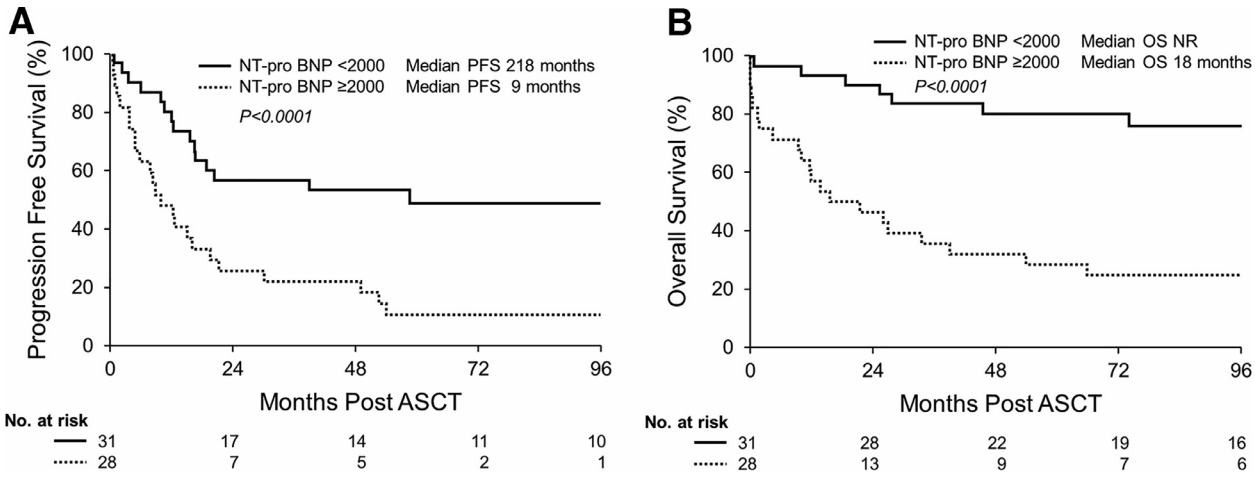

Figure 3. PFS and OS for NT-ProBNP ≥ 2000 versus NT-ProBNP < 2000 pg/mL.

having <3 organs were predictors of better survival in the multivariate model could have been affected.

Skinner et al. [15] evaluated 394 patients who had ASCT for their AL amyloidosis in whom 50% had ≥3 organs involved. They concluded that the number of organs involved should not be an obstacle for ASCT. Clearly, patients who had cardiac involvement did worse with a median survival of 1.6 years compared with 6.4 years ($P < .001$). The mean number of organs in patients who were transplanted was 2.5 with a standard deviation of 1.2. Others have reported their experience in transplanting 522 patients with AL amyloidosis from 1994 to 2011 and 61 (12%) had transplant-related mortality [6]. Of the 61 patients, 54 (89%) had >2 organs involved but also 53 (87%) had cardiac involvement. Comenzo et al. [7] described 25 patients with AL amyloidosis who had ASCT, and 10 patients had ≥3 organs involved. Six (60%) died, and of those 83% had cardiac involvement. The authors concluded that patients with cardiac involvement and more than 2 organs are considered high risk for ASCT. Finally, Rosengren et al. [16] studied the outcomes of 72 patients with AL amyloidosis involving the heart, liver, or kidneys, and only 6 patients (8%) had all 3 organs involved. The median survival was lower for patients who had all 3 organs involved (56 months) compared with those who had only 1 organ involved (135 months). The median survival for patients who had cardiac involvement was 49 months compared with 135 months for those who did not. This suggests that the survival of the patients who had 3 organs involved was lower because heart involvement was much higher in prevalence.

Receiving the standard dose of melphalan (200 mg/m^2) results in deeper response rates and better survival. However, patients need to be selected carefully. In our patients, receiving melphalan at 200 mg/m^2 was an independent predictor for OS using model 1. Tandon et al. [17] concluded that receiving melphalan at 200 mg/m^2 was associated with higher VGPR and CR rates as well as improved PFS and OS. In the study by Skinner et al. [15], 50% of patients had ≥3 organs involved and receiving melphalan at 200 mg/m^2 resulted in a higher likelihood of achieving CR. Patients with higher CR rates had improvement in survival. Similar results were reported by Cibeira et al. [5], showing full-dose melphalan 200 mg/m^2 led to higher CR rates (42.8% versus 24.2%) and improved survival.

In our cohort the melphalan dose was a predictor for OS but not PFS. There may be a number of reasons for this. First, our study had a limited sample size compared with previous reports. Second, there is an inherent selection bias toward selecting patients achieving < VGPR to receive consolidation therapy. It is well established that melphalan dose predicts response, and therefore in our multivariable model, given selection of a great number of patients with < VGPR, hematologic response may have had a more significant effect on survival than melphalan dose. Finally, melphalan dose was a predictor for OS in model 1 and was borderline significant in model 2 ($P = .05$). We believe this is largely related to sample size and loss of power once the Mayo 2012 stage was partitioned into separate categories for NT-proBNP and troponin.

Response assessment after ASCT for AL amyloidosis is typically done at day 100. Hematologic response is predictive of outcomes [13]. In our analysis having at least VGPR at day 100 was predictive for PFS. The median survival for those who had VGPR was 123 months, compared with only 15 months for those who did not. This may suggest that patients who do not achieve at least VGPR post-ASCT should be considered for consolidation therapy. Having any hematologic response was a strong predictor for OS with a median of 143 months for responders, in contrast to 19 months for nonresponders. The value of having deeper responses in predicting outcomes is seen in other studies that evaluated patients who had ASCT

Table 4
Multivariable Analysis for OS

Multivariable Model 1			Multivariable Model 2		
Variable	RR (95% CI)	*P*	Variable	RR (95% CI)	*P*
Hematologic response (≥PR vs. NR), excluding TRM	.12 (.03-.44)	.0015	Hematologic response (≥PR vs. NR), excluding TRM	.1 (.04-.4)	.0009
Mayo 2012 stage (III/IV vs. I/II)	7.7 (2.7-23.0)	.0002	Melphalan 200 vs. 140	.3 (.07-.99)	.05
Melphalan 200 vs. 140	.2 (.06-.73)	.014	NT-proBNP (≥2000 vs. <2000)	4 (1.3-12)	.0133
			Troponin (≥.025 vs. <.025)	2 (.7-5)	.18

PR indicates partial response; NR, no response.

with ≥3 organs involved [5,15]. However, in these studies the analysis was done to look at CR versus no response. In our study any hematologic response was predictive for OS.

Although imaging studies have been shown to be useful in identifying the extent of organ involvement as well as resolution of amyloid deposits, imaging has not been useful in the assessment of prognosis because it is a poor measure of the extent of organ compromise. Early studies have indicated that the rate with which serum amyloid P component clears the bloodstream is a measure of the extent of amyloid deposits; however, this technique is no longer used in any centers. Imaging appears to be incapable of accurate quantification of the extent of amyloid and is not a functional measure of the extent of organ compromise, which is best assessed with blood tests.

Not all patients can undergo ASCT for their AL amyloidosis. In transplant-ineligible patients, chemotherapy can be used to treat patients. Currently, immunomodulators (eg, lenalidomide), proteasome inhibitors (eg, bortezomib), alkylators (melphalan, cyclophosphamide), and steroids can be used. Daratumumab is currently being tested in clinical trials as a first-line therapy in AL amyloidosis patients and has shown promising results. These agents may be considered in patients with multiple organ involvement if they are deemed inappropriate for stem cell transplant. Nevertheless, ASCT has been shown to deepen durable responses with extended follow-up in many patients, and our data in this study supports its use even in patients with multiple organ involvement if the cardiac criteria for stem cell transplant is met.

Our study is limited given the long time period over which it was conducted and the inherent biases of a retrospective review. Although the study was conducted over a long period, at least half of the patients included in the study were transplanted from 2006 onward, corresponding to a time when novel agents were available and used as options to treat AL amyloidosis at our center. Risk stratification with complete data for Mayo 2012 stage and cardiac biomarkers were not available in all patients, and this may have affected our analysis. Despite these limitations, our study highlights the outcomes of patients who had ASCT for AL amyloidosis with ≥3 organs involved, showing that outcomes are primarily driven by cardiac involvement, particularly an NT-proBNP ≥ 2000 pg/mL. Thus, severity of cardiac involvement should be the major criterion for transplanting patients with AL amyloidosis who have more than 2 organs involved and not merely the number of organs involved. Medical insurance providers should not routinely refuse the approval for ASCT in patients who have ≥3 organs involved with AL amyloidosis, if cardiac criteria for safe ASCT is met.

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