

# Effect of Dose-Intensive Intravenous Melphalan and Autologous Blood Stem-Cell Transplantation on AL Amyloidosis–Associated Renal Disease

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**Background:** Dose-intensive intravenous melphalan with autologous blood stem-cell transplantation induces remission of the plasma cell dyscrasia in a substantial proportion of patients with AL amyloidosis. The impact of this treatment on associated renal disease is not known.

**Objective:** To determine the effect of dose-intensive intravenous melphalan and autologous blood stem-cell transplantation on AL amyloidosis–associated renal disease.

**Design:** Prospective cohort study.

**Setting:** Academic medical center.

**Patients:** 65 patients with AL amyloidosis and urinary protein excretion greater than 1 g/24 h who received dose-intensive intravenous melphalan and autologous blood stem-cell transplantation between 1 July 1994 and 30 June 1998.

**Measurements:** 24-hour urinary protein excretion, serum cholesterol level, serum albumin level, creatinine clearance, urine and serum immunoelectrophoresis, and bone marrow biopsy. Renal response was defined as a greater than 50% reduction in urinary protein excretion in the absence of a 25% or greater reduction in

creatinine clearance. Complete hematologic response was defined as absence of detectable monoclonal protein in serum and urine and a bone marrow specimen containing less than 5% plasma cells without clonal dominance of  $\kappa$  or  $\lambda$  isotype.

**Results:** Among the 50 patients who survived for at least 12 months, proteinuria, hypoalbuminemia, and hypercholesterolemia improved during follow-up; 36% met criteria for a renal response. Median 24-hour urinary protein excretion decreased from a baseline value of 9.6 g/24 h to 1.6 g/24 h at 12 months among patients with complete hematologic response, and 71% met criteria for a renal response. Twenty-hour urinary protein excretion did not decrease during follow-up among patients with persistent plasma cell disease, and only 11% had a renal response at 12 months ( $P < 0.001$  for hematologic responders vs. nonresponders).

**Conclusion:** Dose-intensive intravenous melphalan with autologous blood stem-cell transplantation improves the nephrotic syndrome in patients with AL amyloidosis–associated renal disease. The benefit is largely limited to patients achieving eradication of the underlying plasma cell dyscrasia.

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**P**Primary (AL) amyloidosis is a plasma cell dyscrasia in which clonal plasma cells in the bone marrow produce a monoclonal immunoglobulin protein (M protein). The M protein light chains or light-chain fragments form insoluble fibrils with  $\beta$ -pleated sheet configurations, rendering them avid for Congo red dye. The deposition of amyloid fibrils into the extracellular matrix of a variety of tissues results in severe organ dysfunction and poor patient survival.

The kidney is one of the most common sites of amyloid deposition in AL amyloidosis, with clinically evident renal disease occurring in 48% to 82% of patients (1–5). Renal disease associated with AL amyloidosis is usually characterized by the nephrotic syndrome, often with massive proteinuria and refractory peripheral edema (6). The natural history of renal disease associated with AL amyloidosis is persistence of the nephrotic syndrome and progressive decrease in glomerular filtra-

tion rate (5, 7). In one series, one third of patients presenting with renal involvement began long-term dialysis therapy at a median of 13.8 months after diagnosis (2).

Randomized, controlled trials have shown that cyclic oral melphalan and prednisone can prolong the life of patients with AL amyloidosis (1, 4). However, response to this treatment is limited: Serum or urine monoclonal protein levels decrease in only 20% of patients, and the median survival is only 16 to 18 months. Since 1994, we have been using dose-intensive intravenous melphalan with autologous blood stem-cell support to treat selected patients with AL amyloidosis. The goal of this treatment is to eliminate the clonally expanded plasma cells that produce the amyloidogenic light chains, thereby preventing further amyloid deposition into vital organs. In previous studies of this treatment approach, we found that complete remission of the plasma cell dyscrasia occurred in more than 50% of pa-

tients who received 200 mg/m<sup>2</sup> of intravenous melphalan and in more than 40% of patients who received 100 to 140 mg/m<sup>2</sup> of intravenous melphalan followed by autologous stem-cell transplantation (8–10). The objective of the present study was to investigate the effect of this treatment on AL amyloidosis–associated renal disease.

## METHODS

### Patients

In our analysis, we included patients with AL amyloidosis and renal involvement who were treated with dose-intensive intravenous melphalan and autologous blood stem-cell transplantation at Boston University (Boston, Massachusetts) between 1 July 1994 and 30 June 1998. We excluded patients who were dialysis dependent before treatment. Persons who underwent stem-cell mobilization and collection but did not receive intravenous melphalan because of inability to tolerate the former or death before melphalan administration were included in the analysis of treated patients. The diagnosis of AL amyloidosis required both tissue demonstration of amyloid by Congo red staining and evidence of monoclonal immunoglobulin protein in serum, urine, bone marrow, or tissue amyloid deposits. Patients were considered to have renal involvement if urinary protein excretion exceeded 1 g/24 h. The hematologic outcomes of the first 23 of these patients have been reported elsewhere (9, 10), and a brief description of the renal outcome was provided for 13 of the patients (9).

To be eligible for intravenous melphalan with autologous blood stem-cell transplantation, patients needed to be at least 18 years of age, have a Southwest Oncology Group performance status score of 0 to 3, have a left ventricular ejection fraction greater than 0.4, and have supine systolic blood pressure greater than 85 mm Hg. Approximately 40% of patients with AL amyloidosis evaluated at our center during the study period met these eligibility criteria and elected to undergo stem-cell transplantation. The institutional review board of Boston University Medical Center approved the study.

### Treatment

Blood stem cells were mobilized and collected as described elsewhere (9, 10). We used granulocyte colony-stimulating factor (Filgrastim, Amgen, Thousand Oaks, California), 10 to 16 μg/kg of body weight, as the sole mobilizing agent in 59 patients and in combination

with granulocyte-macrophage colony-stimulating factor (Sargramostim, Immunex, Seattle, Washington), 250 μg/m<sup>2</sup>, in 6 patients (10). Seven patients received CD34-selected stem cells (Isolex 300, Baxter Biotech, Irving, California). All other patients received unselected stem cells. Melphalan was administered intravenously during 2 consecutive days at a total dose of 100 to 200 mg/m<sup>2</sup>. Stem cells were infused 24 to 72 hours after completion of melphalan administration.

The dose of melphalan given before autologous stem-cell transplantation was determined on the basis of patient age and clinical status. Eligibility criteria for the highest dose of melphalan (200 mg/m<sup>2</sup>) included age younger than 61 years, left ventricular ejection fraction of at least 0.45, pulmonary diffusion capacity at least 50% of the predicted value, serum creatinine concentration less than 177 μmol/L (2.0 mg/dL), and Southwest Oncology Group performance status score of 0 to 2 (9). Patients who did not meet these criteria were treated with a modified dose (100 mg/m<sup>2</sup> or 140 mg/m<sup>2</sup>, or two cycles of 100 mg/m<sup>2</sup> given 4 to 6 months apart).

### Evaluation and Outcome Measures

Patients were evaluated before treatment, at 3 and 12 months after treatment, and annually thereafter. At each evaluation, 24-hour urinary protein excretion and creatinine excretion were measured and the status of the plasma cell clone was determined by bone marrow biopsy and both serum and urine immunofixation electrophoresis. Complete hematologic response was defined as absence of detectable monoclonal protein by serum and urine immunofixation and a bone marrow biopsy specimen containing less than 5% plasma cells without clonal dominance of κ or λ isotype. Patients with a partial hematologic response (for example, those who showed loss of serum monoclonal protein but persistence of urine monoclonal protein or bone marrow clonality) or no hematologic response were categorized as having persistent plasma cell disease. A renal response was defined as a greater than 50% reduction in 24-hour urinary protein excretion in the absence of a 25% or greater reduction in creatinine clearance.

### Statistical Analysis

Comparisons were performed by using the Wilcoxon test for continuous variables and the Fisher exact

**Table 1. Baseline Clinical Characteristics of Patients with Renal Amyloidosis\***

Characteristic	All Patients (n = 65)	Patients Who Survived for At Least 12 Months (n = 50)	Patients Who Survived Less Than 12 Months (n = 15)	P Value†
Age (range), y	57 (29–77)	56 (29–71)	66 (40–77)	0.024
Men/women, %	57/43	54/46	33/67	>0.2
Light-chain isotype, n (%)				>0.2
κ	8 (12)	7 (14)	1 (7)	
λ	57 (88)	43 (86)	14 (93)	
Organ system involvement, n (%)‡				
1	12 (18.5)	12 (24)	0 (0)	
2	23 (35)	20 (40)	3 (20)	
3	22 (34)	14 (28)	8 (53)	<0.001
4	7 (11)	4 (8)	3 (20)	
5	1 (1.5)	0 (0)	1 (7)	
Melphalan dose, n (%)				
200 mg/m <sup>2</sup>	39 (60)	33 (66)	6 (40)	
140 mg/m <sup>2</sup>	18 (28)	14 (28)	4 (27)	0.010
100 mg/m <sup>2</sup>	8 (12)	3 (6)	5 (33)	
Urinary protein excretion (range), g/24 h	6.7 (1.1–58)	8.0 (1.1–24)	6.4 (2.4–58)	>0.2
Serum albumin level, g/L	27 (11–51)	27 (11–51)	29 (17–38)	>0.2
Serum cholesterol level (range)				0.006
mmol/L	8.6 (0.9–26.3)	10.6 (4.1–26.3)	7.5 (0.9–15.2)	
mg/dL	333 (35–1017)	409 (159–1017)	290 (35–588)	
Serum creatinine concentration (range)				0.079
μmol/L	97 (44–407)	88 (44–398)	106 (71–407)	
mg/dL	1.1 (0.5–4.6)	1.0 (0.5–4.5)	1.2 (0.8–4.6)	
Creatinine clearance (range), mL/min	76 (14–185)	80 (17–185)	50 (14–103)	0.052

\* Values are expressed as medians with ranges unless otherwise indicated.

† For comparisons between those who survived at least 12 months and those who survived less than 12 months.

‡ Organ systems evaluated included renal, cardiac, gastrointestinal tract and liver, peripheral nervous system, autonomic nervous system, and soft tissue.

test for categorical variables. All analyses used a two-tailed significance value of 0.05 and were performed by using SAS for Windows (SAS Institute, Inc., Cary, North Carolina). Confidence intervals for medians were calculated nonparametrically by using the method of Hahn and Meeker (11). Confidence intervals provided for proportions are exact 95% intervals based on the binomial distribution.

### Role of the Funding Sources

The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the paper for publication.

## RESULTS

### Patients

Seventy-two patients with AL amyloidosis–associated renal disease were treated with intravenous melphalan and autologous peripheral blood stem-cell transplantation during the 4-year study period. Seven of these patients were dialysis dependent before treatment and were therefore excluded. The median age of the remaining 65 patients was 57 years; in 88%, the monoclonal

immunoglobulin light-chain isotype was λ (Table 1). Multiorgan involvement was common, and 40% of patients had symptomatic cardiac disease. In most patients, amyloidosis had been diagnosed less than 12 months before intravenous melphalan treatment. Approximately one third of patients had previously been treated with oral melphalan.

The dose of intravenous melphalan preceding autologous stem-cell transplantation was 200 mg/m<sup>2</sup> in 39 patients (60%) and 100 or 140 mg/m<sup>2</sup> in 26 patients (40%). Fifty patients (77%) survived at least 12 months after treatment and were included in the analysis of renal response to treatment. The patients who survived at least 12 months were younger, had fewer organ systems involved, received a higher intravenous melphalan dose, and had higher serum cholesterol concentration at baseline than the 15 patients who died within 12 months (Table 1). Of the 50 patients who survived at least 12 months, 40 (80%) had nephrotic-range proteinuria (>3 g/d) at baseline and 13 (26%) had a baseline serum creatinine concentration of at least 133 μmol/L (1.5 mg/dL).

### Treatment Toxicity

In 15 patients (23%), the serum creatinine concentration doubled or increased by at least 88  $\mu\text{mol/L}$  (1 mg/dL) during the peritransplantation period (defined as 100 days after administration of intravenous melphalan or during stem-cell mobilization or collection). Two of these patients required temporary dialysis. The creatinine concentration returned to its baseline value within 1 to 5 weeks in all but 3 patients; of these 3, 1 died of multiorgan failure 19 days after stem-cell reinfusion, 1 had stabilization of creatinine concentration during the peritransplantation period but subsequently had progressive renal insufficiency requiring initiation of long-term dialysis 13 months after treatment, and 1 had gradual improvement in renal function over the 12 months after treatment. Other treatment-related toxicities included mucositis (53%), peripheral edema (23%), bacteremia (19%), pulmonary edema (18%), elevation in liver enzyme or bilirubin levels (13%), gastrointestinal bleeding (10%), and nongastrointestinal bleeding (10%). None of the patients had sustained dependence on blood product transfusions. Six patients (9%) died during the peritransplantation period. Five of these deaths occurred in patients with symptomatic cardiac disease, and all six occurred in patients who had three or more organ systems affected by amyloid.

### Hematologic Response

Twenty-three of the 65 patients (35%) had a complete hematologic response at 3 months. Among the 50 patients alive at 12 months, 21 (42%) had a complete hematologic response. Six of the 7 patients (86%) with a  $\kappa$  monoclonal protein before treatment had a complete hematologic response at 12 months compared with 15 of 43 (35%) of those with a  $\lambda$  monoclonal protein ( $P = 0.03$ ). Two patients (9.5%) with complete hematologic response at 12 months relapsed after 24 to 48 months follow-up.

### Renal Outcome among All Patients

A renal response occurred at last follow-up in 22 of the 65 patients (34%). A renal response was evident at 3 months in only 3 of 24 patients (13%) who ultimately achieved a renal response and was present at 12 months in 18 of the 24 ultimate responders (75%). Because renal response was delayed for more than 3 months after treatment, we limited the detailed analysis of renal re-

sponse to the subset of patients who survived for at least 12 months.

### Renal Outcome of Patients Surviving for At Least 12 Months

#### All Patients

Among the patients surviving for at least 12 months, improvement in the nephrotic syndrome was evident at 12 and 24 months after treatment (Table 2). The reduction in urinary protein excretion and the corresponding improvement in serum albumin and cholesterol levels were not caused by a decrease in glomerular filtration rate; the changes were similar when patients with at least a 25% reduction in creatinine clearance were excluded from the analysis (data not shown). Criteria for a renal response were met in 18 of 50 patients at 12 months (36%) and 12 of 23 patients at 24 months (52%). Creatinine clearance was maintained at 75% of the baseline value or higher in 68% of patients during follow-up (up to 48 months). Four of the 50 patients (8%) progressed to dialysis dependence 12 to 30 months after treatment.

#### Hematologic Responders vs. Nonresponders

The reduction in proteinuria was greater in the patients with a complete hematologic response than in those with persistent plasma cell disease (Table 2 and Figure). Median 24-hour urinary protein excretion decreased from 9.6 g/24 h (95% CI, 4.2 to 12 g/24 h) at baseline to 1.6 g/24 h (CI, 1.4 to 5.0 g/24 h) at 12 months and 1.4 g/24 h (CI, 0.2 to 3.8 g/24 h) at 24 months in the hematologic responders but did not change appreciably in those with persistent plasma cell disease ( $P = 0.001$  and  $P = 0.008$  for the difference between hematologic responders and nonresponders at 12 and 24 months, respectively).

At 12 months, 71% (CI, 48% to 89%) of patients with a complete hematologic response had a renal response, compared with 11% (CI, 2% to 28%) of those with persistent plasma cell disease ( $P < 0.001$ ). Six patients (2 with complete hematologic response, 4 with persistent plasma cell disease) who did not have a renal response at 12 months achieved a renal response by the 24- or 36-month follow-up. A renal response at 12 months persisted at all subsequent evaluations in 8 of 10 patients (80%) for whom at least 24 months of follow-up data are available. In the 2 remaining patients,

**Table 2. Baseline and Follow-up Measures of Renal Function in Patients Who Survived At Least 12 Months\***

Hematologic Status†	Urinary Protein Excretion (Range)	Serum Albumin Level (Range)	Serum Cholesterol Level (Range)		Serum Creatinine Concentration (Range)		Creatinine Clearance (Range)	Renal Response
			SI Units	Traditional Units	SI Units	Traditional Units		
			g/24 h	g/L	mmol/L	mg/dL		
<b>All patients</b>								
Baseline (n = 50)	8.0 (1.1–23.5)	27 (11–51)	10.6 (4.1–26.4)	409 (159–1017)	88 (44–398)	1.0 (0.5–4.5)	80 (17–185)	NA
3 months (n = 44)	6.9 (0.8–25.0)	30 (15–45)	8.4 (4.7–35.8)	325 (181–1380)	97 (35–796)	1.1 (0.4–9.0)	77 (12–177)	7
12 months (n = 50)	4.3 (0.00–30.0)	34 (5–57)	6.9 (4.7–15.8)	265 (181–609)	115 (62–628)	1.3 (0.7–7.1)	64 (8–171)	36
24 months (n = 23)‡	3.8 (0.00–23.0)	38 (9–50)	6.9 (4.2–16.7)	267 (162–646)	115 (44–725)	1.3 (0.5–8.2)	58 (0.0–165)	52
<b>Patients with complete hematologic response</b>								
Baseline (n = 21)	9.6 (1.1–23.5)	27 (17–51)	11.6 (4.1–18.5)	446 (159–714)	106 (44–398)	1.2 (0.5–4.5)	84 (17–132)	NA
3 months (n = 16)	5.5 (0.8–13.5)	30 (21–43)	6.3 (5.0–35.7)	245 (194–1380)	97 (35–292)	1.1 (0.4–3.3)	81 (14–122)	19
12 months (n = 21)	1.6 (0.0–7.1)	39 (22–57)	6.3 (4.7–12.6)	245 (181–486)	115 (62–318)	1.3 (0.7–3.6)	65 (14–112)	71
24 months (n = 12)	1.4 (0.0–7.3)	40 (31–50)	6.5 (4.2–11.0)	252 (162–426)	106 (44–354)	1.2 (0.5–4.0)	68 (14–165)	75
<b>Patients with persistent plasma cell disease</b>								
Baseline (n = 29)	7.0 (1.7–21.6)	23 (11–41)	9.3 (4.5–26.4)	360 (172–1017)	88 (62–301)	1.0 (0.7–3.4)	77 (24–185)	NA
3 months (n = 28)	7.8 (0.8–25.0)	28 (15–45)	9.6 (4.7–17.8)	371 (181–686)	97 (62–796)	1.1 (0.7–9.0)	73 (12–177)	0
12 months (n = 29)	5.9 (0.2–30.0)	27 (5–53)	8.4 (4.7–15.8)	324 (182–609)	115 (62–628)	1.3 (0.7–7.1)	62 (8–171)	11
24 months (n = 11)	9.5 (0.6–23.0)	24 (9–47)	7.3 (5.1–16.7)	281 (197–646)	141 (62–725)	1.6 (0.7–8.2)	53 (0–149)	27
P value at 12 months§	0.001	0.002		0.051		>0.2	<0.001	<0.001
P value at 24 months§	0.008	0.031		>0.2		0.188	>0.2	0.039

\* Values are expressed as medians with ranges unless otherwise indicated. NA = not applicable.

† Status of plasma cell dyscrasia at 12 months.

‡ Of the 27 patients not evaluated at 24 months, 3 died between 12 and 24 months and 24 had not yet reached 24 months of follow-up.

§ Comparison between patients with complete hematologic response and those with persistent plasma cell disease. At baseline and 3 months, no differences were statistically significant.

loss of renal response was preceded by evidence of a relapse of the plasma cell dyscrasia after a complete hematologic response.

Patients with complete hematologic response appeared to have better preservation of creatinine clearance than patients with persistent plasma cell disease. Two of 21 patients (9.5%) with complete hematologic response at 12 months had at least a 25% reduction in creatinine clearance at last follow-up. Both of these patients had a hematologic relapse before the decrease in renal function. In contrast, 15 of 29 patients (52%) in whom the plasma cell dyscrasia persisted at 12 months had at least a 25% reduction in creatinine clearance at last follow-up ( $P = 0.002$  for remitters vs. nonremitters). All four patients who progressed to dialysis dependence during follow-up had persistent plasma cell disease when evaluated 12 months after treatment.

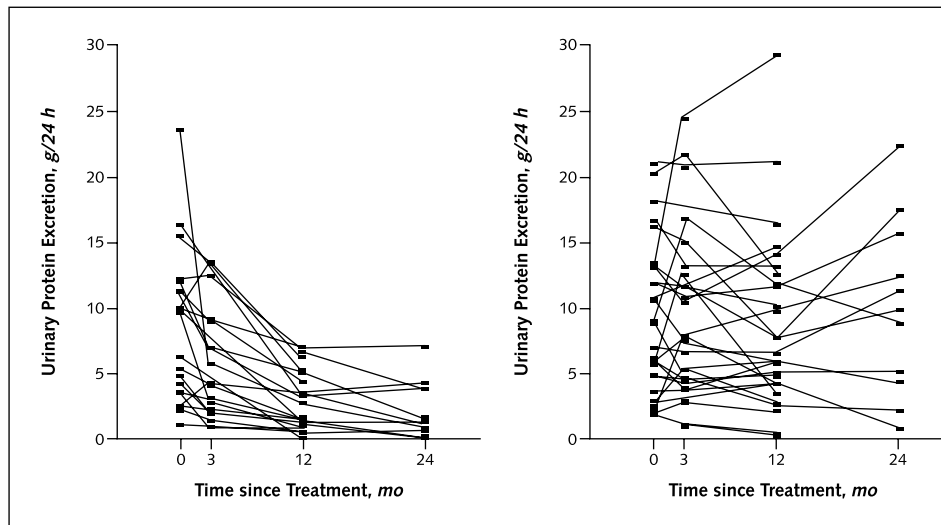
## DISCUSSION

We have demonstrated a reduction in proteinuria following dose-intensive intravenous melphalan and au-

tologous blood stem-cell transplantation in patients with AL amyloidosis-associated renal disease. A renal response, defined as a greater than 50% reduction in 24-hour urinary protein excretion in the absence of at least a 25% reduction in creatinine clearance, occurred at 1 year in 36% of surviving patients and was sustained during subsequent follow-up in the vast majority. Sixty-eight percent of surviving patients maintained a creatinine clearance at 75% of the baseline value or greater, and only 8% progressed to dialysis dependence in up to 4 years of follow-up.

The reduction in proteinuria after dose-intensive intravenous melphalan with autologous stem cell transplantation was much more pronounced in patients who achieved remission of the plasma cell dyscrasia than in those with persistent disease. Among the complete hematologic responders, median 24-hour urinary protein excretion decreased from 9.6 g/24 h before treatment to 1.6 g/24 h and 1.4 g/24 h at 12 and 24 months, respectively. At 12 months, 71% of patients with a complete hematologic response met criteria for renal response. In

Figure. Change in 24-hour urinary protein excretion in individual patients surviving at least 12 months.



Left. Patients with complete hematologic response at 12-month follow-up ( $n = 21$ ). Right. Patients with persistence of the plasma cell dyscrasia at 12-month follow-up ( $n = 28$ ). One patient with persistence of the plasma cell dyscrasia is not represented because data for 24-hour urinary protein collection were not available at 12 months.

contrast, among patients with persistence of the plasma cell dyscrasia, urinary protein excretion decreased only modestly at 12 months, and a renal response at that time point was seen in only 11% of patients.

Renal outcomes after conventional treatment for AL amyloidosis have been described elsewhere. Skinner and colleagues (4) reported a reduction in proteinuria in approximately 10% of patients treated with oral melphalan and prednisone, and Kyle and coworkers (1) found an 18% renal response rate (defined as  $\geq 50\%$  reduction in proteinuria at last follow-up in the absence of progressive renal failure) among similarly treated patients. In both of these studies, approximately 18% of all treated patients began dialysis during 5- to 10-year follow-up. Although the data are not reported, it is likely that this percentage was considerably higher among patients with renal involvement at baseline. We were not able to directly compare our results of treatment with dose-intensive intravenous melphalan with results of previous studies of oral melphalan and prednisone due to differences in eligibility criteria and outcome measures. However, the strong relationship we found between renal response and achievement of a complete hematologic response suggests that treatments that eradicate the plasma cell dyscrasia are more likely to result in improvement in renal disease.

The requirement for stable creatinine clearance in our definition of renal response minimizes the possibility that an observed reduction in proteinuria is the result of a decrease in glomerular filtration rate rather than a reflection of restoration of selective permeability of the glomeruli. Previous studies of treatment for AL amyloidosis did not incorporate a measure of glomerular filtration rate into the definition of renal response (4); did not specify the measure of glomerular filtration rate used (1, 9, 10); or used serum creatinine concentration (12), which can be affected by the change in muscle mass that often occurs over time in patients with systemic amyloidosis.

The mechanism underlying the observed reduction in proteinuria is not known. It is presumed that deposition of amyloid fibrils into the mesangium and glomerular basement membrane produces structural alterations that interfere with the selective permeability properties of the normal glomerulus. It is possible that arresting deposition of new amyloid may allow endogenous cells and proteases to degrade existing amyloid deposits. Although a reduction in renal amyloid after treatment has not been demonstrated histologically in this study or in a previous report (13), such a process is supported by reductions in tissue amyloid content by scintigraphy using  $^{125}\text{I}$ -labeled human serum amyloid P component

(14, 15) and the delay in the renal response relative to the hematologic response that we observed. Alternatively, it is possible that the amyloidogenic light chains filtered by the glomerulus or circulating cytokines associated with the plasma cell dyscrasia have a direct, reversible toxic effect on glomerular epithelial cells.

Experience from a variety of other proteinuric renal diseases and animal models of glomerular disease suggests that reducing proteinuria has a beneficial effect on long-term renal outcome (16–19). Thus, in addition to decreasing the systemic sequelae of the nephrotic state, the reduction in proteinuria resulting from intravenous melphalan and autologous blood stem-cell transplantation may directly improve renal survival. Creatinine clearance was preserved in most patients in our cohort who achieved a complete hematologic response. Although encouraging, this finding must be viewed as preliminary given the short duration of follow-up in many of the patients.

Dose-intensive intravenous melphalan with autologous blood stem-cell transplantation is associated with significant toxicity. Most patients had some type of short-term toxicity, and 9% died within 100 days of treatment. Two surviving patients had sustained renal impairment that was believed to be treatment-related. It should be noted that most patients in this cohort had multiorgan system disease, and it is these patients who carry the highest risk for treatment-related morbidity and death (9).

Our study has limitations. The lack of a control group limits assessment of the efficacy of the treatment protocol. However, given the poor renal outcome of untreated AL amyloidosis, as well as historical experience with oral melphalan and prednisone (1, 4), treatment with dose-intensive intravenous melphalan seems to offer substantial benefit to patients with renal disease. Our eligibility criteria and the specialized nature of our treatment center may reduce the generalizability of our findings. However, our study sample included patients with a broad range of disease manifestations and disease severity. Both functionally well and critically ill patients were enrolled. Therefore, our study group represents the spectrum of patients with AL amyloidosis.

We have demonstrated a clear improvement in AL amyloidosis–associated renal disease following dose-intensive intravenous melphalan and autologous blood stem-cell transplantation. The benefit seems to be largely

restricted to patients achieving complete eradication of the plasma cell dyscrasia. Our results suggest that improvement in end-organ function is a reasonable expectation of aggressive AL amyloidosis treatment.

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