Acute Renal Insufficiency After High-Dose Melphalan in Patients With Primary Systemic Amyloidosis During Stem Cell Transplantation

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• ***Background:*** **Patients with primary systemic amyloidosis (AL) have a poor prognosis. Median survival time from standard treatments is only 17 months. High-dose intravenous melphalan followed by peripheral blood stem cell transplant (PBSCT) appears to be the most promising therapy, but treatment mortality can be high. The authors have noted the development of acute renal insufficiency immediately after melphalan conditioning. This study was undertaken to further examine its risk factors and impact on posttransplant mortality.** ***Methods:*** **Consecutive AL patients who underwent PBSCT were studied retrospectively. Acute renal insufficiency (ARI) after high-dose melphalan was defined by a minimum increase of 0.5 mg/dL (44 μmol/L) in the serum creatinine level that is greater than 50% of baseline immediately after conditioning. Urine sediment score was the sum of the individual types of sediment identified on urine microscopy.** ***Results:*** **Of the 80 patients studied, ARI developed in 18.8% of the patients after high-dose melphalan. Univariate analysis identified age, hypoalbuminemia, heavy proteinuria, diuretic use, and urine sediment score (>3) as risk factors. Age and urine sediment score remained independently significant risk factors in the multivariate analysis. Patients who had ARI after high-dose melphalan underwent dialysis more often (P = 0.007), and had a worse 1-year survival (P = 0.03).** ***Conclusion:*** **The timing of renal injury strongly suggests melphalan as the causative agent. Ongoing tubular injury may be a prerequisite for renal injury by melphalan as evidenced by the active urinary sediment. Development of ARI adversely affected the outcome after PBSCT. Effective preventive measures may help decrease the treatment mortality of PBSCT in AL patients.** ***Am J Kidney Dis*** **45:102–111.**

INDEX WORDS: Primary amyloidosis; nephrotic syndrome; renal insufficiency; peripheral blood stem cell transplant (PBSCT); melphalan; urine sediment.

PRIMARY SYSTEMIC amyloidosis (AL) is a rare and fatal disease characterized by fibrillary deposition of immunoglobulin light chain fragments. The accumulation of amyloid in the extracellular matrix leads to progressive multiorgan failure and ultimately death. Prognosis of systemic disease is poor with a median survival of 13 months after diagnosis.[1] Patients with symptomatic cardiac dysfunction fare the worst, followed by those with hepatic involvement and then renal failure.[2] No cure currently exists for AL. Treatments with melphalan and prednisone or other chemotherapies provide only limited success. Despite occasional reports of prolonged survival, data from controlled clinical trials showed only about 20% to 30% of the patients achieved a therapeutic response.[3-8] This poor response rate translates to a marginal benefit in the median life expectancy from 13 months to 17 months.[5-7] Recently, autologous peripheral blood stem cell transplantation (PBSCT) after dose-intensive intravenous melphalan has been used successfully in the treatment of AL. Several groups reported promising results suggesting superiority of PBSCT over conventional chemotherapy.[9-12] However, it does come with a price as treatment-related mortality can reach as high as 43%, even higher than for other hematologic diseases.[12-14] Differences in organ dysfunction may be responsible for this disparity.[15] Non-AL patients who are candidates for PBSCT rarely have visceral organ dysfunction, whereas visceral organ involvement is required for consideration of intensive therapy for AL. Risk of death after PBSCT is highest among AL patients with poor cardiac function, multiorgan involvement, or renal insufficiency.[15-17]

The development of acute renal failure (ARF) increases the mortality in any illness, but it is particularly ominous after hematopoietic stem cell transplantation (HSCT).[18-21] Mortality rates as high as 88% have been reported if dialysis is

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required after HSCT.[22,23] Because many AL patients have preexisting renal insufficiency, they may be more susceptible to renal injury during stem cell transplant. In fact, we have noted an acute decline in renal function in some patients immediately after conditioning with high-dose melphalan. These patients appear to have an increase in morbidity and mortality. The purpose of this retrospective study is to investigate the incidence, risk factors, and impact of this particular type of renal insufficiency in AL patients after PBSCT.

METHODS

Patients

Consecutive patients with AL who underwent PBSCT at our institution between March 1996 and October 2001 were selected for this study. Medical records were reviewed retrospectively. Amyloidosis was diagnosed histologically in all patients by demonstration of apple green birefringence after Congo red staining of tissue biopsies. AL was confirmed by demonstration of light chains in tissue by immunofluorescence corresponding to the monoclonal (M) protein in the serum or urine or the clonal expansion of plasma cells in the bone marrow. Secondarily, familial and localized amyloidosis was excluded. Those who started dialysis before conditioning were also excluded from the study. Written informed consent was obtained before the study entry for all patients. Both the protocol and consent form were approved by the Institutional Review Board at the Mayo Foundation in accordance with the Declaration of Helsinki.

Laboratory Studies

Glomerular filtration rate (GFR) was determined either by 24-hour creatinine clearance or nonradioactive iothalamate clearance corrected for body surface area.[24] Serum albumin level was determined by serum protein electrophoresis. Urine samples were analyzed in 3 phases, chemistry by the Hitachi 911 (Roche-Hitachi, Basel, Switzerland), osmolarity by freezing point depression via MicroOsmett 2430 (Precision Systems Inc, Natick, MA), and microscopy by the Yellow IRIS (International Remote Imaging Systems, Inc, Chatsworth, CA) to screen for urinary sediment. Samples with abnormal protein to osmolarity ratio or abnormal urine sediment were checked manually by a trained laboratory technician. Each cell type and cast was identified and recorded individually. The urine sediment score represents the sum of the following: red blood cell (>1/high-power field [hpf]), white blood cell (>3/hpf), hyaline cast, granular cast, waxy cast, oval fat body, fat in cast, free fat, renal epithelial cell, and bacteria for a maximum score of 10.

Clinical data were extracted from medical records and a laboratory database. These included patient characteristics, pre- and posttransplant laboratory values, nephrotoxic drug exposure, dialysis, and survival. If multiple GFR and 24-hour urine protein measurements were obtained, the one closest to the transplant date was recorded. Daily measurements of serum creatinine (Scr) were obtained after conditioning until the patient was dismissed.

Table 1. Baseline Patient Characteristics

	Group 1	Group 2	*P*
No.	15	65	
Men	60%	56.9%	0.83
Age*	59	54	0.04
Mass* (kg)	77.7	72.8	0.31
Scr* (mg/dL)	1.2	1.0	0.16
GFR* (mL/min/1.73 m^2)	61	67	0.58
Cockcroft-Gault* (mL/min)	65.4	75.1	0.33
Serum albumin*	1.8	2.8	0.01
β-2 microglobulin* (μg/mL)	2.6	2.1	0.08
Cyclosporine use	0%	10.8%	0.97
Diabetics	13.3%	6.2%	0.35
Diuretic use	86.7%	49.2%	0.017
24-hour urine protein* (g/d)	7.0	3.1	0.013
Urine sediment score*	5	1	0.0004

NOTE. To convert Scr in mg/dL to μmol/L, multiply by 88.4; GFR in mL/min to mL/s, multiply by 0.01667.

*Values expressed as median.

Stem Cell Mobilization and Conditioning

Stem cells were mobilized using either pulse cyclophosphamide (3 g/m^2) and granulocyte-macrophage colony-stimulating factor (5 μg/kg/d; 33 patients) or granulocyte colony-stimulating factor alone (47 patients). Conditioning consisted of either melphalan (100 to 200 mg/m^2) alone (n = 63) or melphalan (140 mg/m^2) with total body irradiation (2 Gy twice daily for 3 days; n = 17. The full dose of melphalan was given on a single day in all but 2 patients who received divided dose in consecutive days. Urine alkalization with 5% dextrose with 100 mEq of sodium bicarbonate was infused before and after stem cell infusion. Standard premedications with 100 mg of hydrocortisone, 50 mg of diphenhydramine, 20 mg of furosemide, and 1 g of acetaminophen were administered to every patient before transplantation. Additional furosemide was administered as needed to maintain urine output and avoid volume overload.

Definition of Acute Renal Insufficiency After High-Dose Melphalan

In this study, acute renal insufficiency (ARI) was defined as an increase of greater than 0.5 mg/dL (44 μmol/L) in Scr that is more than 50% above baseline. The increase in Scr must occur within 48 hours of melphalan infusion to be considered related to high-dose melphalan. Group 1 consisted of patients who met the above criteria. Patients in group 2 did not develop ARI, did not meet criteria, or had other explainable causes for the elevation in Scr.

Statistical Analysis

Statistical analysis was performed using the SAS software package. Survival rate was estimated using the method of Kaplan and Meier. Logistic regression was used to identify