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Blood stem cell transplantation as therapy for primary systemic amyloidosis (AL)

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Summary:

This study investigated the response rate and toxicity of blood cell transplantation as treatment for primary amyloidosis (AL). Twenty-three patients had stem cells collected between November 1995 and September 1998. Conditioning included melphalan and total body irradiation in 16 and melphalan alone in 4. Three patients did not undergo stem cell infusion because of poor performance status. Two died of progressive amyloid at 1 and 3 months. One patient is alive on hemodialysis. Fourteen males and six females (median age, 57 years) underwent transplantation. Renal, cardiac (by echocardiography), peripheral neuropathy or liver amyloidosis occurred in 14, 12, 3, and 1, respectively. Echocardiography demonstrated an interventricular septal thickness ⩾15 mm in six patients, five of whom died post transplantation. Three patients died of progressive amyloidosis at 7, 7, and 21 months. Thirteen patients are alive with a follow-up of 3 to 26 months. Twelve (60%) fulfilled the criteria of a hematologic or organ response. Severe gastrointestinal tract toxicity was seen in five (25%). We conclude that blood cell transplantation for amyloidosis had a much higher morbidity and mortality compared with transplantation for myeloma. The best results appear to occur in patients with nephrotic syndrome as the only manifestation of their disease. *Bone Marrow Transplantation* (2000) **26,** 963–969.

Keywords: stem cell transplantation; multiple myeloma; amyloidosis; monoclonal protein; nephrotic syndrome; congestive heart failure

Amyloidosis is the clinical disorder that results from the deposition of insoluble fragments of immunoglobulin light or heavy chains.[1] The subsequent disruption of organ function resulting from the extracellular deposition of these fragments ultimately leads to death. Chemotherapy has been used for more than 20 years.[2] Treatment aimed at interrupting synthesis of the precursor immunoglobulin light chain produces responses that ultimately translate into improved survival for this disease.[3,4] Unfortunately, the response rate rarely exceeds 30%, and the median survival of all patients ranges between 12 and 18 months.[5,6] The low response rate to chemotherapy likely reflects the relatively small number of nonproliferative plasma cells in the bone marrow of patients with this disease. Recently, reports of allogeneic,[7,8] syngeneic,[9] and autologous[10,11] stem cell transplantation have documented objective response with disease regression. This study was undertaken to assess the overall response rate and the toxicities associated with stem cell transplants for amyloidosis.

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Materials and methods

Amyloidosis was confirmed with a tissue biopsy in all patients. Sections stained with Congo red demonstrated green birefringence when viewed under polarized light. Patients with secondary, familial, or localized amyloidosis were excluded. Patients with AL whose disease was limited to only cutaneous involvement, purpura, or carpal tunnel syndrome were excluded. To ensure adequate ability to procure stem cells, patients could not have received >500 mg total lifetime dose of melphalan.[12] Patients had to have either a demonstrable monoclonal (M) protein in the serum or urine or a clonal population of plasma cells in the bone marrow. Their Eastern Cooperative Oncology Group performance status must have been 0 to 2. Serum creatinine concentration had to be <2.5 mg/dl.[13] The alkaline phosphatase concentration had to be <4 times the institutional upper limit of normal. All patients gave written informed consent before study entry, and the protocol and consent form were both approved by the Institutional Review Board of the Mayo Foundation in accordance with the Declaration of Helsinki.

All patients underwent baseline evaluation of the amyloidosis, which included amyloid stains of bone marrow and fat, immunofixation of serum and urine, and an echocardiogram to estimate the severity of amyloidosis. The response criteria for amyloidosis have been defined.[4] These are the same response criteria that we have used in previous studies of treatment in patients with amyloid.[4,6,14] The organ response criteria required a 50% decrease of 24-h urine protein excretion in the absence of an increase in serum creatinine concentration in patients with renal amyloidosis. In patients with hepatic involvement, response required a 50% reduction in the serum alkaline phosphatase

level with no increase in transaminase value, bilirubin value, or liver size. Echocardiographic regression of amyloidosis of the heart required a 2 mm decrease in the thickness of the interventricular septum or an increase of 20% in the ejection fraction. Patients with overt multiple myeloma were excluded. In our experience, the majority of patients with bone marrow plasmacytosis of less than 30% never develop any of the cardinal features of multiple myeloma, such as myeloma cast nephropathy or myeloma bone disease. Therefore, a diagnosis of myeloma is not made simply on the basis of a plasmacytosis of 10% to 30% in the absence of any other clinical features of multiple myeloma. Patients with moderate to severe congestive heart failure were not eligible for this protocol.

Hematologic response criteria conformed to those established for multiple myeloma.[15] All patients who had a serum or urine M protein were monitored for changes in the size of the M peak. Patients who had only free light chain detectable in the serum or in the urine had immunofixation performed to monitor for presence or absence of the light chain. M component response criteria required a 50% reduction of a peak in the serum or urine after transplantation. If only a light chain was detectable, a response required complete eradication of the light chain by immunofixation.

Three patients had prior exposure to melphalan to a total dose of 400 mg, 392 mg, and 60 mg, respectively. Five patients had been treated with high-dose dexamethasone before being evaluated for stem cell transplantation. None of the patients had evidence of a response before stem cell collection. Stem cells were mobilized in all patients but one by using cyclophosphamide (1.5 g/m^2) given intravenously daily for 2 days. On day 3, granulocyte–macrophage colony-stimulating factor was initiated (5 μg/kg per day) and continued until stem cells were collected. Leukapheresis began when the total white blood cell count recovered to $>500/\mu$l. The remaining patient received granulocyte colony-stimulating factor (10 μg/kg per day), with stem cell collection commencing on day 5.

An average of 14 liters of blood (4-h leukapheresis) was processed per procedure. The target progenitor cell number was 5×10^6 CD34-positive cells/kg. This target was achieved in all patients but one who had previously been treated with 400 mg of melphalan and achieved a CD34-positive cell dose of 2.75×10^6/kg. Conditioning consisted of either melphalan (140 mg/m^2) with total body irradiation (2 Gy twice daily for 3 days) or melphalan (200 mg/m^2).

Supportive care after stem cell infusion included daily use of an oral quinoline antibiotic combined with fluconazole. Because of mucositis and anorexia, all but two patients received total parenteral nutrition during the course of the transplantation. It was common to see fluid retention after growth factors were begun in patients with nephrotic syndrome. Albumin was regularly required but was not part of the protocol.

Results

There were 23 patients who had their stem cells successfully collected. There were no deaths attributable to stem cell mobilization. Three patients tolerated mobilization poorly, and it was decided not to proceed with transplantation. One patient with mild congestive heart failure became performance status 3 after stem cell mobilization and died of progressive cardiac amyloid 3 months after collection. In one patient with advanced hepatic amyloidosis, progressive ascites developed. It was elected not to proceed with conditioning, and he died 1 month after collection. The third patient developed severe gastrointestinal (GI) tract toxicity; transplantation was deferred. She developed end-stage renal disease and is alive on hemodialysis 1 year after initial mobilization.

Twenty patients have undergone transplantation, and their characteristic pretransplant hepatic, renal, and echocardiographic features are given in Table 1. Transplantation occurred between January 1996 and November 1998. No patients were lost to follow-up. The serum and urine immunoglobulin findings are given in Table 2. An M protein was detectable in 18 of the 20 patients. The remaining 2 had a clonal population of plasma cells in the bone marrow: one 16% λ and one 12% κ. The symptomatic amyloid syndrome at diagnosis is given in Table 3. Fourteen of the 20 underwent transplantation because of dominant renal amyloid. Twelve patients had positive echocardiographic evidence of amyloid, but none were in moderate to severe

Table 1 Characteristics of study patients

Characteristic	*Number or range*	*Median*	*Percent abnormal*
Sex	14 M/6F		
Age, years	37–70	57	
Albumin, g/dl	1.1–4.2	2.5	$70 < 3$ $25 < 2$
Creatinine, mg/dl	0.6–2.4	1.1	$30 > 1.3$
Alkaline phosphatase, U	87–347	171	$20 > 250$
Serum M protein, g/dl ($n = 12$)	0.1–1.68	0.1	$8 > 1.5$
24-h urine protein, g	0.03–11.54	3.33	$70 > 3$
Urine M protein, g/day ($n = 16$)	0.05–1.27	0.45	$13 > 1$
Marrow cIg+	1–43	11	
Echo IVS, mm	9–18	13	$30 \geqslant 15$
EF, %	54–80	68	

cIg+ = cytoplasmic immunoglobulin positive cells (ie, plasma cells); Echo = echocardiography; EF = ejection fraction; IVS = interventricular septum.

Table 2 Serum and urine immunoglobulin findings

Protein	*Patients, no.*	
	Serum	*Urine*
None	8	4
Aλ	1	
Gκ	1	
Gλ	3	
κ	1	2
λ	6	14

No serum or urine M protein in 2 patients: one had 16% plasma cells, all λ, and one had 12% plasma cells, all κ.

Table 3 Clinical syndromes in AL

Syndrome	*Patients, %*
Renal (nephrotic)	70
Cardiac by echocardiography	60
Peripheral neuropathy	15
Hepatic	5
Splenic rupture	5
Autonomic neuropathy	10

Of the 10, seven, and three patients who had 1, 2, or 3 organ systems involved, nine, four, and 0, respectively, are alive.

congestive heart failure, with the lowest recorded ejection fraction at 54%.

The diagnosis of amyloid was established histologically in all patients. Three patients had a positive rectal biopsy, nine had a positive renal biopsy, five had a positive endomyocardial biopsy, 17 had amyloid deposits in the bone marrow, 14 had amyloid deposits in the fat, and one had a positive sural nerve biopsy. Sixteen of the 20 patients (80%) were conditioned with melphalan and total body irradiation. The melphalan was administered on day −4 as a single dose. High-dose melphalan (200 mg/m^2) was chosen for four patients (20%). The entire dose was given on day −1 as a single infusion over 1 h. The stem cells were infused in all patients on day 0. Two had pacemakers, contraindicating radiation. In the remaining two, the treating physician elected to give high-dose melphalan alone because of concerns regarding mucositis.

Overall, the requisite number of stem cells was procured with a median of four leukaphereses (range 1 to 10). The patient who required 10 leukaphereses had the highest prior exposure to melphalan and ultimately was transplanted with more than 2×10^6 CD34-positive cells/kg. The median time from the initiation of leukapheresis to day 0 of transplant was 31 days (range 10 to 91 days).

One patient died suddenly (day +6) and was not evaluable for engraftment. The remaining 19, however, all achieved engraftment. A median of 500 neutrophils was achieved at a median of 9 days post transplant (range 7 to 19 days), and only one patient took >12 days to achieve 500 neutrophils. A platelet count of 20 000/μl was achieved at a median of 10 days (range 6 to 29 days). Only three required >14 days to achieve 20 000 platelets. A platelet count of 50 000/μl was achieved at a median of 13 days (range 7 to 70 days). Five of the patients required >15 days to achieve 50 000 platelets.

Transplantation resulted in a high proportion of patients with unexpected morbidity and mortality. At this time, seven of the 20 patients have died (35%), four as a direct result of transplant-related complications (Table 4). One patient died suddenly on day 6 after transplantation of presumed asystole or ventricular fibrillation. Autopsy demonstrated moderate cardiac deposition of amyloid deposits. A second patient died of multiorgan failure and was found to have advanced multiorgan amyloidosis at autopsy. One patient, who had severe peripheral and autonomic neuropathy before transplant, developed progressive disability post transplant and died of aspiration pneumonia, secondary to a protracted bedridden status, before day 100. This patient had a 50% decrease in urinary protein excretion. The fourth patient died of pneumonia, with no organism isolated 2 months after transplantation. All four patients had engrafted promptly after stem cell infusion. Three additional patients died, two of progressive congestive heart failure at 6.5 and 21 months after transplantation and one of pneumonia that precipitated acute renal failure with subsequent cardiac decompensation and death 7 months after transplantation. Two patients, both of whom had severe nephrotic-range proteinuria with >6 g of protein loss per day, developed acute renal failure after conditioning for transplantation. Their pretransplant creatinine values were 2.1 and 2.4 mg/dl. One episode of acute renal failure was attributed to bacteremia post transplant. The patient recovered and eventually became dialysis independent. The second was thought to be a consequence of multiple factors, which included intravascular volume contraction from hypoalbuminemia in combination with moderate renal insufficiency pretransplant. The patient died 4 days later. Overall, the number of days in the hospital ranged from 3 to 78, with a median hospital stay of 22 days (day −4 to day +17).

Thirteen patients (65%) had documented infections after transplantation. Six (30%) had blood cultures positive for coagulase-negative staphylococcus. Two patients had enterococcal bacteremia. Two patients had proven *Acinetobacter* infection, one had micrococcus, one had *Pseudomonas*, and one had *Escherichia coli*.

Five patients (25%) had unexpected cardiac arrhythmias during collection and transplantation. One patient developed atrial fibrillation and flutter with variable atrioventricular block during stem cell mobilization. Two patients developed supraventricular tachycardia and atrial fibrillation and two developed atrial flutter with 2-to-1 block on day 7, day 3, day 3, and day 18 post transplant. Although these cardiac arrhythmias were not responsible for the death of any of the five patients, the development of the arrhythmias complicated the care of four of the patients during critical periods of neutropenia. All five patients were known to have cardiac amyloidosis pretransplant. One with a septal thickness of 11 mm had an endomyocardial biopsy demonstrating amyloid. The other four had septal thicknesses of 13, 13, 13, and 15 mm. Three had low-voltage electrocardiograms typical of amyloidosis.

An unexpected development was marked GI tract toxicity. Overall, five of the 20 patients (25%) developed marked GI tract toxicity: four of the 16 who received melphalan and total body irradiation and one of the four who received melphalan alone. Two of the patients required placement of percutaneous feeding gastrostomies to maintain nutrition, and two required protracted support with central parenteral nutrition. One of these four also had severe GI tract bleeding that precipitated multiorgan failure. The fifth patient never received enteral or parenteral nutritional support but ultimately lost 25 kg of body weight before nutritional recovery occurred and weight began to return to pretransplant baseline.

A response was seen in 12 patients (60%) (Table 4). In six patients, the nephrotic syndrome improved significantly. The reduction in urinary protein excretion exceeded 4.9 g/day in all responding patients with nephrotic syn-

Table 4 Transplant outcome in 20 patients conditioned

Age, year/sex	*Response*	*Status, mo*	*Cause of death*
70/M	N	D, 2.0	Post-BMT pneumonia
59/M	Urine κ resolved 24° urine 6.5 → 0.3 g/d	32	
47/M	24° urine 9.7 → 3.6 g/d	31	
59/F	Urine λ resolved 24° urine 7.4 → 0.1 g/d	26	
43/F	GI pseudo-obstruction requiring cpn which resolved Subsequent cardiac progression	D, 21.4	Progressive CHF
39/M	Liver size ↓ 6 cm	20.7	
48/F	N	D, 6.5	Progressive CHF
52/M	N	D, 7.1	Pneumonia, ARF, advanced cardiac AL at autopsy
58/M	N	17.2	
65/M	Mixed (urine protein decreased 6000 → 2470 mg/d but neuropathy worsened)	D, 2.3	Aspiration, progressive autonomic failure
37/M	Serum and urine λ resolved 24° urine 11.5 → 4.0 g/d	16	
44/F	Serum IgAλ 1680 → 96 mg/dl	D, 1.0	Multiorgan failure, advanced AL at autopsy
62/M	N	D, 0.2	Sudden cardiac death, moderate cardiac AL at autopsy
58/F	24° urine 7.9 → 3.0 g/d	10.0	
47/M	Serum and urine λ resolved	6.3	
40/M	24° urine 8.8 → 2.4 g/d	7.6	
65/M	Marow PC: 28 → 5% Serum and urine κ resolved	3.9	
57/M	Urine λ resolved	3.3	
60/M	N	5.5	
63/F	Serum G λ 1.43 → 0.2 mg/dl Urine 4395 → 1005 mg/d	4.0	

ARF = acute renal failure; BMT = bone marrow transplant; CHF = congestive heart failure; cpn = central parenteral nutrition; D = died; GI = gastrointestinal; N = no response; PC = plasma cells; 24° urine = 24-h urine protein excretion.

drome, with no increase in creatinine concentration. In every case this decrease exceeded 50% of pretransplant urinary protein excretion. One patient who had symptomatic GI tract pseudo-obstruction pretransplant requiring parenteral nutrition returned to a normal nutritional state. One patient had resolution of hepatomegaly, and eight patients (three of whom had organ responses listed above) had significant hematologic responses with marked reduction or elimination of the synthesis of monoclonal immunoglobulins (Table 4). At this time, 13 of the 20 patients remain alive (65%) with follow-up of 3 to 30 months (median, 16 months). In the 12 responders, the median time to response was 4 months and three took >9 months.

Discussion

Therapy for AL continues to be unsatisfactory. Melphalan and prednisone therapy was first used for the management of this disorder in 1975, based on a regimen with known activity in the management of multiple myeloma.[14] In the years since then, the median survival of patients with amyloidosis treated in this way did not exceed 2 years.[16] Only a minority of patients respond to this therapy and therefore the treatment did not have a profound impact on survival.

Stem cell transplantation has been shown to improve the complete response rate and the overall survival of patients with multiple myeloma.[17,18] It is, therefore, reasonable to consider stem cell transplantation in the management of amyloidosis. Moreau *et al*[19] published a report of a 46-year-old patient with amyloidosis and congestive heart failure who survived 17 months after a bone marrow transplant, with evidence of a hematologic response measured by eradication of λ light chains from the urine. Syngeneic transplantation has also been reported after failed melphalan and prednisone therapy in a 32-year-old patient, with improvement in autonomic neuropathy and urinary protein loss.[9] The clinically related but histologically distinct light chain deposition disease has also been treated successfully with cyclophosphamide and total body irradiation.[20] Comenzo *et al*[21] reported five patients, all of whom had regression of their amyloidosis after stem cell transplantation using melphalan-only conditioning. In a subsequent update of 25 patients,[10] 11 of 17 survivors experienced improvement of amyloid-related organ involvement. When the information was updated to 50 patients in abstract form,[22] 21 were evaluated 12 months post therapy: 13 had improved and six had stable amyloid-related organ involvement. Important prognostic factors for adverse overall survival included >1 organ system involved, cardiac involvement, and age >55 years.

Moreau *et al*[11] recently reported on a multicenter study of 21 patients. They found an unexpectedly high death rate from toxic reactions of 43% (nine of 21), but 10 of the 12 survivors achieved a response. We likewise saw an unexpectedly high death rate from toxic reactions, with an excellent response rate in those patients surviving the procedure. Gillmore *et al*[23] also reported in abstract form on 27

patients who underwent high-dose melphalan therapy, with 30% treatment-related deaths due to multiorgan failure. They also saw GI tract hemorrhage as an unexpected complication in two patients. A clinical response was seen in 57% of patients, with documented regression of amyloid by serum amyloid P scanning in 50% of patients. They reported that important prognostic factors for a successful outcome included a creatinine clearance >30 ml/min, urinary protein loss <3 g, absence of congestive heart failure, absence of hepatomegaly, and absence of peripheral neuropathy.

The optimal mobilization scheme for patients with amyloid is unknown. In multiple myeloma, the stem cell yields appear to be greater when chemotherapy is combined with a growth factor. In patients receiving 10 μg of growth factor per kg per day, we have seen severe episodes of fluid retention, progressive edema, bilateral pleural effusions, and ill-defined pulmonary syndromes that we have not seen using growth factor combined with cyclophosphamide at the modest dose of 3 g/m^2. We have not seen any unusual complications of the cyclophosphamide during the neutropenic period and our anecdotal experience suggests that the use of cyclophosphamide with the lower dose of growth factor of 5 μg/kg/day may be desirable.

We believe that when carefully applied, stem cell transplantation can be effective in the management of patients with amyloid, but careful selection of patients is required. From 1983 to 1997 we evaluated 1288 patients with biopsy-proven amyloid. When applying the criteria of no overt multiple myeloma, age $\leqslant$70 years, echocardiographic septal thickness $\leqslant$15 mm with an ejection fraction greater than 55%, serum creatinine $\leqslant$2 mg/dl, alkaline phosphatase $\leqslant$3 times normal, and direct bilirubin $\leqslant$2 mg/dl, only 207 (16%) would have fulfilled the eligibility criteria and been candidates for stem cell transplantation.

Our death rate of 20% from toxic reactions far exceeds the treatment-related mortality we have seen in autologous transplantation for multiple myeloma (2%), Hodgkin's disease, and non-Hodgkin's lymphoma. This suggests there are features of patients with amyloidosis that are unique compared with other patients with hematologic malignancy undergoing transplantation. The unexpected development of acute renal failure may be related to the marked volume contraction typically seen in patients with hypoalbuminemia; intravascular volume contraction is seen as a consequence of hypoalbuminemia due to high urinary protein losses. In addition, such patients are frequently treated with diuretics that increase vascular volume depletion. The extreme GI tract toxicity was also significant, requiring protracted nutritional support for four patients. Schulenburg *et al*[24] reported on a patient with AL who died of GI tract perforation, presumably related to amyloid infiltration of submucosal vessels in the bowel. There were two deaths due to GI tract hemorrhage in the group reported by Gillmore *et al*[23] as well. Routine endoscopic biopsy of the intestinal tract reveals amyloid deposits in 80% of patients. The overwhelming majority of patients do not have GI tract symptoms pretransplantation. It is difficult to determine whether routine endoscopic biopsy should be part of the pretransplantation evaluation of patients with amyloidosis if they have no symptoms referable to the GI tract. The impact of GI tract involvement with amyloid on transplant-associated GI tract morbidity is difficult to assess accurately before transplant. However, the treating physician must be aware of an unusually high prevalence of GI tract morbidity. Kazmi and Schey[25] reported four transplants for amyloidosis, with two deaths: one catastrophic GI hemorrhage and one case of pneumonia a year post transplant.

Ultimately, the response rate that we saw exceeds our previous experience using conventional-dose chemotherapy. In general, the response rate in all patients treated with melphalan and prednisone is 30%, and when patients exclusively with amyloid nephrotic syndrome without renal insufficiency are evaluated, their response rate is 40%. In this study, 12 of the 20 (60%) demonstrated a response using identical criteria, suggesting that dose-intensive chemotherapy may produce superior responses if the patients can survive conditioning. It therefore becomes important to determine which patients are optimal candidates for conditioning. It is likely that this will be a highly selected group. Currently, transplantation would not be appropriate for the majority of patients with amyloidosis. Others have suggested that patients older than 55 years are not suitable candidates.[26] In the six patients older than 60 years who had transplants, two had a single organ involved, two had two organs involved, and two had three organs involved. The deaths occurred in both patients with three-organ involvement and one of the two with two-organ involvement. Three of the patients had cardiac involvement and this may have played a role in the poor outcome in older patients. Conditioning in four of the six included radiation. Two of the four died. Two of the patients received melphalan only and one of the two died. We do not believe that the total body radiation played a role in the toxic death rate. The two oldest patients were 65 and 70 years old, and both died before day 100, suggesting that age can play an important role in patient selection. In addition, patients with moderate cardiac amyloidosis should not be considered candidates for transplantation, which would eliminate one patient in five. Six of the patients we treated with transplantation did not have overt congestive heart failure, but did have an echocardiogram demonstrating an interventricular septal thickness $\geqslant$15 mm, and five of these six have died, suggesting that significant echocardiographic evidence of amyloid, even in the absence of congestive heart failure, should be considered a contraindication to transplant. The high proportion of supraventricular tachyarrhythmias during collection and transplantation was also associated with pretransplant echocardiographic evidence of amyloid, further complicating the management of these patients in the hospital. Similar cardiac toxicity has been reported with the use of standard-dose chemotherapy in patients with cardiac amyloidosis.[27]

The ideal conditioning pretransplantation of patients with amyloid is not established. We did observe a higher prevalence of mucositis as well as the need for total parenteral nutrition in the patients receiving total body irradiation. However, it does not appear that the conditioning had an impact on outcome. Outcome was related primarily to the extent of cardiac involvement and the number of organs involved at the time of transplantation.

The protracted time to recognize a response in this dis-

Table 5 Guidelines for selection of transplant patients

Absolute contraindication
Clinical congestive heart failure
Total bilirubin >3.0 mg/dl
Echocardiographic ejection fraction <55%
Relative contraindication
Serum creatinine >2.0 mg/dl
Interventricular septal thickness >15 mm
Age >60 years
More than two visceral organs involved

order is not surprising. The fact that three patients took >9 months to fulfill the criteria for response fits with the known pathogenesis of amyloidosis. Presumably, transplantation quite quickly stopped the synthesis of immunoglobulin light chains by the bone marrow plasma cells. Once precursor protein production is interrupted, however, it takes some time for amyloid deposits to be resorbed by the body. With conventional chemotherapy, it regularly takes a year for amyloid deposits to resorb, reflecting the low turnover rate of amyloid *in vivo*.[28]

Even given the potential restrictions of age, multiorgan involvement, and echocardiographic cardiac involvement, there will still be a subset of patients who appear to have an improved outcome when treated with high-dose therapy. An Eastern Cooperative Oncology Group study is currently under way to determine whether our results can be duplicated at many other centers. For now, clinicians should be cautious and need to be highly selective in determining which patients should be considered for stem cell transplantation.

Our study has insufficient follow-up and numbers to assess the true survival rate, risk of relapse, potential for long-term complete remission, and risk of late myelodysplasia. We report our results because we believe it is important for centers that do a small number of transplants in patients with amyloidosis to be aware of the unique toxicities that can be seen. The restrictions outlined above in terms of age, cardiac involvement, multiorgan involvement, and renal insufficiency should be applied in the selection process (Table 5).

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