

Myeloablative chemotherapy and stem cell transplantation in myeloma or primary amyloidosis with renal involvement

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Background. High-dose chemotherapy and stem cell transplantation are being applied increasingly to the treatment of selected patients with multiple myeloma or primary systemic amyloidosis. Stem cell transplantation presents unique challenges to the nephrologist because of the high prevalence of renal involvement in myeloma and the issues that are associated with high-dose chemotherapy in patients with the nephrotic syndrome due to renal amyloid.

Methods. We review the published literature on stem cell transplantation in patients with reduced renal function.

Results and Conclusions. The specifics of transplantation pertaining to patients with renal amyloid nephrotic syndrome are discussed in detail.

MULTIPLE MYELOMA

Multiple myeloma accounts for 1% of malignancies and 10% of hematologic malignancies. In the United States, the incidence of multiple myeloma is approximately 4.1/100,000 per year, and approximately 15,270 individuals in the United States developed and 11,070 died of this disorder in 2004 [1]. The median age of patients at diagnosis is 66 years. The disease remains incurable except for the small subset of patients who are candidates for and survive allogeneic transplantation. A small globulin spike is found in the urine in 60% of multiple myeloma patients, and frequently monoclonal light chains are toxic to the renal tubule, causing so-called myeloma cast nephropathy with tubular obstruction, anuria, and azotemia. Patients with multiple myeloma frequently develop renal insufficiency due to hypercalcemia. The median urine monoclonal protein in patients with multiple myeloma is 0.48 g/24 hours, and

two thirds of patients excrete more than 200 mg/day. The median serum creatinine concentration at presentation is 106 $\mu\text{mol/L}$, 29% of patients present with a serum creatinine value from 106 to 176 $\mu\text{mol/L}$, and 19% have a creatinine value greater than 176 $\mu\text{mol/L}$ at presentation [2]. Renal failure does not appear to impact the response rate to therapy, but if renal failure does not respond to therapy for myeloma, survival is shorter [3].

The standard therapy for multiple myeloma has moved increasingly toward autologous stem cell transplantation. Two prospective randomized studies have shown a survival advantage for patients who receive a single autologous transplant compared with conventional chemotherapy [4, 5], and one prospective randomized study [6] has shown a survival advantage for patients who receive tandem (two consecutive) stem cell transplantation compared with a single autologous stem cell transplantation. The first randomized study showing the superiority of transplantation included only a few patients with renal dysfunction, but the serum creatinine concentration had to be less than 150 $\mu\text{mol/L}$ before transplantation. Recently, tandem transplantation showed a superior survival compared with oral chemotherapy in patients aged 60 to 70 years [7].

In the case of high-dose chemotherapy with stem cell transplantation in patients with renal dysfunction, anecdotal and case series provide information regarding toxicity, but there are no prospective studies that definitively clarify the effect high-dose chemotherapy with stem cell transplantation has in these patients with regard to quality of life or overall survival. As a point of reference, reversal of renal failure in myeloma patients treated with conventional chemotherapy resulted in survivals not different from that of treated patients without renal failure in a study of 88 patients with a serum creatinine concentration more than 180 $\mu\text{mol/L}$. Though improvement in renal function was seen in 51% of patients and in only 24% of those with cast nephropathy, a survival prolongation was not seen compared with those conventionally treated patients whose renal function did not improve [3]. Because dose-intensive chemotherapy can be administered to selected patients whose age is up to 73 years [8],

Key words: high-dose chemotherapy, multiple myeloma, nephrotic syndrome, primary amyloidosis, renal failure, stem cell transplantation.

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Table 1. Transplantation in myeloma patients with renal failure

Reference	Number of patients	Treatment-related mortality%	Event-free survival	Overall survival	Number on dialysis
Ballester et al [15]	6	17	4 (6-39 months)		4
San Miguel et al [16]	14	29		56% at 3 years	
Tosi et al [17]	6	0	5/6 responders		1
Mikhael et al ^a	21	14			11
Badros et al [18]	81		51% at 3 years	60% at 3 years	38
Sirohi et al ^b	6	50			6

^aMikhael JR, Mazaheri R, Sutton DM, et al: Feasibility of high-dose therapy and autologous stem cell transplantation in multiple myeloma patients with severe renal failure [abstract]. *Blood* 98 (Pt 1):199a, 2001.

^bSirohi B, Powles R, Kulkarni S, et al: Feasibility of administering high-dose melphalan (HDM) with autotransplantation in myeloma patients on dialysis [abstract]. *Blood* 98 (Pt 2):399B, 2001.

the majority of patients with multiple myeloma are candidates for high-dose therapy. In the Mayo Clinic series, the median age at transplantation is 57 years and only 4% are age 70 years or older. Younger patients with human leukocyte antigen (HLA)-matched donors may be candidates for allogeneic stem cell transplantation, which poses additional challenges. Care of these patients will directly involve collaboration between hematologists and nephrologists [9].

Autologous stem cell transplantation in myeloma patients with renal insufficiency

The primary chemotherapeutic agent administered to patients with multiple myeloma is melphalan at doses ranging from 140 to 200 mg/m². Doses as high as 280 mg/m² have been administered, with a suggestion that dose escalation may result in higher response rates [10]. The pharmacokinetics of high-dose melphalan indicate that the half-life and the area under the curve are correlated significantly with creatinine clearance, although there are great interindividual variations. Renal insufficiency does not lead to a large decrease in melphalan clearance compared to the interindividual variations in systemic clearance [11]. In a prospective study, six patients whose creatinine clearance was less than 40 mL/min, including five on chronic hemodialysis, received 200 mg/m² of melphalan over 2 consecutive days. The median half-life of the melphalan was 1.1 hours, and the clearance of the drug was 27.5 L/hour in patients whose creatinine clearance was less than 40 mL/min. Renal insufficiency had no negative impact on the quality of stem cell collections, stem cell engraftment, mucositis, or overall survival but did result in longer hospitalization [12]. Novel conditioning regimens can also cause problems unique to myeloma patients. The use of ¹⁶⁶holmium-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonic acid (DOTMP) plus melphalan to condition patients with multiple myeloma can cause renal endothelial damage and renal failure due to a thrombotic microangiopathy [13]. In one study, 30% of patients conditioned with ¹⁶⁶holmium-containing reg-

imens experienced grade 2 to 4 renal toxicity that led to dialysis-dependent renal failure in 14 of 83 patients (17%) treated. Hemorrhagic cystitis is also seen in patients conditioned with holmium-containing regimens [14]. Six patients with multiple myeloma and renal insufficiency, including 4 on dialysis, were conditioned with busulfan and cyclophosphamide followed by autologous stem cells. One of the patients who achieved a complete response showed progressive recovery of renal function with a reduction in creatinine from 678 μmol/L to 352 μmol/L. Renal failure produced no difficulty in the procurement of stem cells [15] (Table 1).

Bladé et al [19] reported on outcomes in 94 myeloma patients with renal failure treated with standard-dose chemotherapy. When patients who died within the first 2 months of therapy were excluded, there were no significant differences in the response rates between patients with renal failure and those with normal renal function. The serum creatinine level, however, did correlate with survival. In patients whose creatinine value was greater than 177 μmol/L, the overall median survival was 8.6 months [19].

The Spanish myeloma group reported on patients with myeloma and renal insufficiency who underwent stem cell transplantation. The first group presented at diagnosis with renal insufficiency but had recovered renal function at the time of stem cell transplantation. The second group included patients who had persistent renal insufficiency at the time of transplantation. Treatment-related mortality in the renal failure patients depended on three variables: (1) Eastern Cooperative Oncology Group performance status of 3 or more, (2) a hemoglobin concentration of less than 95 g/L, and (3) a serum creatinine value greater than 440 μmol/L. Renal failure was not an exclusion factor for transplantation. No dose modification of chemotherapy was made, which may have contributed to the high treatment-related mortality [16].

The myeloma group from Bologna, Italy, reported their results on six renal failure patients. No patients showed a decline of renal function through the transplantation. The median pretransplantation creatinine clearance for the six patients was 20 mL/min. The median

posttransplantation creatinine clearance for the six patients was 60 mL/min. Pretransplantation, four of the six patients had a creatinine clearance less than 30 mL/min. Posttransplantation, only one patient had a creatinine clearance less than 30 mL/min [17].

The Princess Margaret Hospital group reported outcomes in renal failure patients. The mean creatinine value for patients not on dialysis was 232 $\mu\text{mol/L}$ (range 177 to 343 $\mu\text{mol/L}$). Median duration of hospitalization was 21 days. None of the patients who were dialysis dependent at the time of transplantation had significant improvement in their renal function. None of the patients who were dialysis independent developed worsening renal function from the transplantation procedure [abstract; Mikhael JR, et al, *Blood* 98 (Pt 1):199a, 2001].

The largest experience has been reported from the Myeloma Center of Little Rock, Arkansas. Eighty-one patients with serum creatinine concentration greater than 176 $\mu\text{mol/L}$ were reported. There was no difficulty in mobilizing stem cells. Sixty patients, 27 of whom were on dialysis, received full-dose melphalan of 200 mg/m^2 . Because of excessive toxicity, subsequent patients received a reduced dose of 140 mg/m^2 . Patients who received transplants and the melphalan dose of 200 mg/m^2 had a significantly higher incidence of pulmonary complications (57% vs. 17%), hypotension (25% vs. 5%), and mucositis (93% vs. 67%). The patients on hemodialysis had a higher incidence of pulmonary complications (53% vs. 19%), neurologic complications (47% vs. 6%), and skin rash (75% vs. 10%) than those not on hemodialysis. Two patients discontinued dialysis after stem cell transplantation. Dialysis dependency did not affect event-free or overall survival [18].

The transplant-related mortality was 6% after the first and 16% after the second transplant. The complete hematologic response rate was 27% after the first transplant and 38% after the second transplant. There was no difference in complete response or event-free survival between melphalan 200 mg/m^2 and melphalan 140 mg/m^2 , and the latter was less toxic.

Twenty-seven of our patients whose serum creatinine concentration was greater than 176 $\mu\text{mol/mL}$ have undergone transplantation. Five of the 27 died before day 100. Four of the five had advanced multiply relapsed disease, and their deaths were not related directly to the renal failure. Two of the five had pulmonary aspergillosis related to extensive prior therapy with corticosteroids before transplantation. One patient died on day -1 of fulminant sepsis. Median survival posttransplantation is 27 months.

Among 42 patients with renal failure and 84 pair-matched controls with normal renal function, response rates and 3-year actuarial survivals were comparable in the two groups [20]. Patients on dialysis, when condi-

tioned appropriately, can have similar outcomes to patients with less-impaired renal function [21, 22].

Although the disease-free survival appears comparable in renal-impaired myeloma patients and patients with normal renal function, recovery of renal function is uncommon, and patients with end-stage renal disease (ESRD) continue to be dialysis dependent. Two patients with myeloma who required hemodialysis at diagnosis became dialysis independent after high-dose melphalan and autografting. Low serum albumin concentration may predict transplant-related complications in renal failure patients treated with high-dose melphalan, an issue particularly relevant to amyloid patients [23].

Six myeloma patients on dialysis (age 50 to 65 years) received melphalan 200 mg/m^2 in four and melphalan 140 mg/m^2 in two. Grade 3 to 4 mucositis developed in all of the patients, and four had bacteremia. Atrial fibrillation developed in four. Three of four patients receiving melphalan 200 mg/m^2 died of toxic responses in the first month. Both of the patients receiving melphalan 140 mg/m^2 survived [abstract; Sirohi B, et al, *Blood* 98 (Pt 2):399B, 2001].

The current transplantation guidelines for patients with myeloma developed by the Cancer Care Ontario Practice Guidelines Initiative acknowledge that autologous transplantation is feasible in patients with serious renal dysfunction, but no prospective randomized studies indicate a survival benefit compared with conventional therapy. They did not recommend that transplantation be considered standard therapy for patients whose creatinine value was greater than 150 $\mu\text{mol/L}$ until randomized trials demonstrate a survival benefit for these patients. If renal dysfunction seen at diagnosis improves with induction therapy, the patients should be considered subsequently for high-dose therapy [24].

Morbidity is acceptable in patients who are on stable dialysis or who have stable mild chronic renal insufficiency when they come to transplantation. The situation is altered dramatically if acute renal failure develops during transplantation, requiring dialysis support during the first 30 days after conditioning. In a cohort of 97 consecutive allogeneic blood and marrow transplant patients, 20 (21%) developed acute renal failure, Bearman grade 3. All died by day +132. The renal failure was a contributing cause or the primary cause of death in 18 of the 20 patients developing renal insufficiency. The presence of renal insufficiency strongly favors an autologous stem cell source [25].

Rarely, the kidney is a target for the development of graft-versus-host disease after allogeneic transplantation for myeloma. Nephrotic syndrome and membranous glomerulonephritis developed in one patient as manifestations of graft-versus-host disease after transplantation for multiple myeloma [26].

A patient who received a HLA-mismatched cadaveric donor renal transplant [27] for mesangial capillary glomerulonephritis developed multiple myeloma as a posttransplantation lymphoproliferative disorder 10 years after his kidney transplantation. Ultimately, the patient received an autologous peripheral blood stem cell transplant followed by a continuous complete remission 2 years later. Epstein-Barr virus-related multiple myeloma occurring after solid organ transplantation has been reported recently in three patients and must be considered a rare complication of solid organ transplantation [28].

In summary, there are no randomized studies that answer the question of whether renal failure patients receiving high-dose therapy benefit in terms of relapse-free and overall survival. Renal failure patients do not have impaired ability to mobilize stem cells or to engraft. Whether the disease control achieved by high-dose therapy outweighs increased treatment-related mortality cannot be proved, but it appears that reducing the dose of melphalan to 140 mg/m² reduces the morbidity to acceptable levels for most patients with renal failure. These patients should be considered for immediate stem cell mobilization followed by high-dose chemotherapy, as outcomes in heavily pretreated patients result in mortality up to 21%.

AMYLOIDOSIS

Amyloidosis involving the kidney produces even greater challenges for the nephrologist. Nephrotic syndrome is the most common indication for autologous stem cell transplantation and is associated with the best outcome. Fifty-six percent of patients with amyloidosis excrete more than 1 g of protein in a 24-hour period, and 44% manifest nephrotic-range proteinuria. The high prevalence of hypoalbuminemia predisposes them to postconditioning renal insufficiency and excessive fluid shifts. The entire process surrounding autologous peripheral blood stem cell transplantation—mobilization, chemotherapy conditioning, stem cell infusion, and the chemotherapy toxicity period—poses unique challenges, including excessive fluid retention, cardiac arrhythmia, renal failure, and gastrointestinal hemorrhage.

Among the first 171 patients who received autologous peripheral blood stem cell transplants for primary systemic amyloidosis at Mayo Clinic, the serum creatinine concentration ranged from 53 to 345 $\mu\text{mol/L}$. The median serum creatinine value was 97 $\mu\text{mol/L}$, and 9% of patients with a serum creatinine value greater than 177 $\mu\text{mol/L}$ received transplants. The 24-hour urine protein excretion ranged from 20 mg to 26 g/24 hours. The median 24-hour urine protein loss for the entire group was 3.7 g, 64% or 110 patients lost more than 1 g of protein in the urine for 24 hours, and 56% or 95 patients lost more than 3 g for the 24-hour period. Median age at transplantation was

55 years, ranging from 31 to 71 years. The serum albumin value ranged from 10 to 44 g/L (median 28 g/L). Twenty-five percent of patients had an albumin value less than 20 g/L, values that are quite relevant to the subsequent toxicity seen. We and others have reported the ability of high-dose therapy followed by autologous blood stem cell transplantation to produce regression of nephrotic syndrome in patients with amyloidosis. In fact, the frequency of response is at least double that seen with more traditional chemotherapy such as melphalan and prednisone. A response has a profound impact on outcome. Among our 171 patients, 117 responded (68%), and only 12 of those have died to date. The median survival of responders has not been reached, but their median survival will exceed 6 years. Response is an important predictor of overall survival.

Response in patients with amyloidosis is a two-part concept. Responses are often divided into hematologic and organ. The former uses the same monoclonal protein and bone marrow variables used in determining response in patients with multiple myeloma. The latter involves predefined improvements in organ function—in the case of renal, a 50% reduction in the total urine protein. Two patients with biopsy-proven renal primary amyloidosis underwent stem cell transplantation, and urinary protein excretion decreased from 7 g/day to less than 2 g/day. A repeat renal biopsy was performed in both patients, and persistent glomerular amyloid was present [29].

Unlike multiple myeloma (high plasma cell burden), most patients with amyloid (low plasma cell burden) do not receive induction chemotherapy before moving to stem cell mobilization, bone marrow conditioning, and finally hematopoietic stem cell transplantation. An exception is a phase 1/2 study from a group from The Netherlands involving vincristine, doxorubicin, and dexamethasone (VAD) chemotherapy induction. Thirty-eight patients with amyloidosis were evaluated. Of 12 patients who received transplants, renal involvement was present in 11. Seven of the nine surviving patients showed hematologic responses, with organ responses in six of the nine survivors documented by serum amyloid P scintigraphy. Worsening of renal function requiring transient dialysis was seen in one patient. There was one death from a myocardial infarction after the first course of VAD [30].

The Amyloidosis Center in Pavia, Italy, reported that cardiac involvement, hypoalbuminemia, and dysautonomia with hemodynamic instability increased the procedural risk of mobilization and collection of stem cells. During collection, 39% of patients had hypotension, and 6.4% of the episodes were life threatening [abstract; Perotti CG, et al, *Blood* 102 (Pt 2):415B, 2003]. We have also found that the morbidity is higher in patients who undergo stem cell mobilization using chemotherapy and a growth factor compared with growth factor alone [31]. Fatal cardiac arrhythmias developed in one patient

Table 2. Transplantation for renal amyloidosis

Reference	Number of patients	Number with renal amyloidosis	Comments	Outcome
Meier et al ^a	8	3	Median protein loss 15.7 g/day	6.6 g/day post-stem cell transplant
Snanoudj et al [39]	1	1		Complete response
Casserly et al [40]	15	15 (end-stage renal disease)	Treatment-related deaths (<i>N</i> = 2)	Complete response (<i>N</i> = 8)
Mollee et al ^b	48	32	Transplanted (<i>N</i> = 20), seven deaths	3-year survival 56%
Blum et al [41]	13	7	Treatment mortality 15%	2-year survival 47%

^aMeier P, Bakr M, Frossard V, et al: Renal outcome in dose-intensive melphalan therapy and autologous stem cell transplantation for AL amyloidosis [abstract]. *J Am Soc Nephrol* 13:669A, 2002.

^bMollee PN, Wechalekar AD, Pereira DL, et al: Autologous stem cell transplantation (ASCT) in primary systemic amyloidosis (AL): The impact of selection criteria on outcome [abstract]. *Blood* 100 (Pt 1):435A, 2002.

whose serum creatinine value was 338 $\mu\text{mol/L}$ during the infusion of dimethyl sulfoxide cryopreserved stem cells [32].

Mortality in autologous stem cell transplantation for amyloid is high, and in our patient population it is 12%. The serum β_2 -microglobulin value, the serum creatinine value, and the number of organs involved are associated with treatment-related mortality. Three of our patients developed postchemotherapy renal insufficiency and died of dialysis-related complications. Of the 21 treatment-related deaths seen among the 171 patients, the serum creatinine value of these patients ranged from 79 to 343 $\mu\text{mol/L}$, with a median of 114 $\mu\text{mol/L}$. Four of the 21 patients who had treatment-related deaths had a pretransplantation creatinine value more than 176 $\mu\text{mol/L}$ [33]. The best outcomes were seen in patients with single-organ involvement, predominantly patients with renal amyloid (115 of the 171) [31].

Transplantation for amyloidosis is associated with unique toxicities that are not generally seen in patients who receive transplants for other hematologic malignancies such as multiple myeloma [34]. Toxic megacolon has been reported in four separate amyloidosis patients, two of whom had renal amyloid deposits [35]. Intestinal bleeding is seen in 5% of patients, toxic renal responses in 8%, and mucositis grade 3 to 4 in 21%, higher than anticipated for patients who undergo transplantation with nonamyloidotic disease [36]. The risk of death from toxic response from two or more organ dysfunctions has approached 75%. In one review, treatment-related mortality was 30% due to multiorgan failure, gastrointestinal tract hemorrhage, sepsis, and cardiac complications [37].

The most common serious posttransplantation complication appears to be postconditioning renal insufficiency. Postconditioning renal insufficiency is defined as a 50% increase in serum creatinine concentration within 48 hours of conditioning. Age, hypoalbuminemia, heavy proteinuria, diuretic use, and a urine sediment score greater than 3 were risk factors. Patients with postconditioning renal insufficiency were dialyzed more often and had an inferior 1-year survival. The timing of postconditioning renal insufficiency suggests melphalan is the

causal agent. Tubular injury may be a prerequisite for postconditioning renal insufficiency, as evidenced by the urinary sediment observed. Postconditioning renal insufficiency appears to be specific to amyloidosis and is not described in other disorders. The exact nature of the injury remains unclear. It was seen in 15 of 80 patients (19%) in our cohort [38].

The justification for subjecting patients to a treatment that carries such potential for morbidity is the excellent reported outcomes (Table 2). Eight patients were treated with high-dose melphalan. All eight developed acute renal failure during the peritransplantation period at a median of 12 days after stem cell infusion. These eight required hemodialysis for a median of 6 weeks. All patients recovered renal function. Serum albumin concentration increased in all patients with nephrotic-range proteinuria. Creatinine clearance did not decrease. Acute renal failure, when it occurs posttransplantation, is often a reversible complication. The development of acute renal failure does not preclude an excellent outcome [abstract; Meier P, et al, *J Am Soc Nephrol* 13:669A, 2002]. In one patient with renal amyloidosis whose pretransplantation serum creatinine concentration was 89 $\mu\text{mol/L}$ rapidly progressive multiorgan failure developed, including anuria and septic shock on day +8. The renal failure resolved. A hematologic complete response was attained, and a complete remission of nephrotic-range proteinuria was achieved [39].

The group at Boston University reported on 15 patients who came to transplantation with amyloidosis-associated ESRD. The median survival for the eight responders was 4^{1/2} years. Five patients with a hematologic complete response have undergone or are awaiting renal transplantation. It is feasible for amyloid patients who are on chronic hemodialysis to undergo transplantation [40].

Patients who are scheduled recipients of a renal allograft are in a special situation relating to stem cell transplantation. One of the impediments to long-term successful renal transplantation in amyloidosis is recurrent disease in the allografted kidney [42]. We have applied stem cell transplantation as a means to delay or reduce the risk of recurrent amyloid in a transplanted

kidney. At the Mayo Clinic to date, seven patients have been recipients of high-dose therapy, stem cell transplant, and renal transplant with the goal of reducing precursor light chain production, thereby reducing the risk of amyloid recurrence. All seven patients were alive from 1.1 to 39.5 months (median 18.7 months). It is too early to draw any conclusions as to whether this combination of renal and stem cell transplantation will provide superior clinical outcomes, but feasibility and safety have been established. It is our perception that patients who receive a stem cell transplant after renal transplantation actually have reduced morbidity associated with the procedure. Four of our patients who received transplants had doses of melphalan of 200 mg/m², and three had 140 mg/m². All patients required hospitalization from 4 to 18 days. Renal transplantation either after stem cell transplantation or preceding planned stem cell transplantation is a consideration for patients who develop end-stage renal disease and have no amyloid outside the kidney [43].

Deciding which patients are candidates for high-dose therapy is critical. Selection of poor-prognosis patients inevitably results in high treatment-related morbidity and mortality. In a single-center report on 48 patients, only 26 were deemed stem cell transplant candidates. They were significantly younger, had a better performance status, and had a trend to better cardiac function than patients who were not considered candidates for stem cell transplantation. Five patients died during mobilization, and there was one mobilization failure. Treatment-related mortality of 35% was reported. Intent-to-treat organ response in the kidney was 46%. The 3-year overall post-stem cell transplantation survival was 56%. The presence of nephrotic syndrome predicted a better 3-year overall survival [abstract; Mollie P, et al, *Blood* 100 (Pt 1):435A, 2002].

In an attempt to reduce the morbidity associated with stem cell transplantation, we and others have attempted a risk-adapted approach to therapy [34]. Patients are classified by performance status, number of organs involved, and severity of organ involvement into categories of candidates for full-dose therapy, candidates for reduced-dose therapy, and candidates for conventional therapy.

In an attempt to further reduce toxic organ responses, an experimental conditioning regimen of total body irradiation alone was developed for patients with amyloidosis. The total body irradiation dose was 550 cGy given in one dose at 30 cGy/min. Noncardiac toxic organ response was mild. The hematologic complete remission rate was 45%. Conditioning with total body irradiation alone is feasible and may result in fewer treatment-related complications. Renal responses to the conditioning regimen of total body irradiation were documented with a reduction in 24-hour urine protein loss from 12 g to 1.2 g, 17 g to 4.7 g, and 16 g to 1.1 g. Two other patients had

urinary protein responses from the nonnephrotic range to less than 1 g/day [40].

The patient selection that occurs in determining which patients are suitable candidates for transplantation introduces inherent selection bias and, therefore, we anticipate survival for patients receiving a transplant is better than that for those who do not receive a transplant simply as a result of selection features alone [44]. In this cohort, patients who would have been eligible to receive a transplant but were treated conventionally had a median survival of 42 months and a 5- and 10-year survival of 36% and 15%, respectively. These results are clearly superior to what would be expected in terms of survival in an unselected cohort of patients with amyloid. Seventy-three percent of this group had renal amyloidosis, and 37% had renal amyloid as the only manifestation of disease. In spite of the inherent superiority of patients eligible for transplantation, our recently published case-control series suggested that patients who do receive a transplant have a better survival than those patients treated conventionally [45].

In conclusion, stem cell transplantation for patients with renal amyloidosis, including those with end-stage renal failure, is feasible and results in significant palliation and an improvement in quality of life [46], particularly in those who achieve a hematologic complete response. Although the existing data support the use of high-dose therapy in selected patients, the selection inherent in choosing patients represents a favorable prognostic group no matter what treatment they receive. No phase 3 study data are available to conclusively prove a response or survival benefit of stem cell transplantation over conventional therapy in amyloidosis.

Randall-type light chain deposition disease clinically resembles light chain amyloidosis. Nephrotic syndrome and ESRD are common. We reviewed the long-term outcome of renal transplantation in our patients with light chain deposition disease. Among seven patients, light chain disease recurred in five. One patient remains alive on dialysis, four have died, and only one remains recurrence free [47]. Renal allograft survival is reduced significantly unless measures have been taken to reduce light chain production. In an effort to treat the underlying plasma cell proliferative disorder, 11 young patients with light or heavy chain deposition disease received high-dose therapy. No toxic deaths occurred. A decrease in monoclonal immunoglobulin levels was observed in eight patients. Organ manifestations improved in six patients, including renal, cardiac, and hepatic responses. Histologic regression of monoclonal immunoglobulin deposits was documented in the heart, liver, and skin. No manifestations related to the monoclonal immunoglobulin deposits occurred or recurred in any patient. Consideration of high-dose therapy is reasonable in younger patients with light chain deposition disease. Suppression of light

chain production may render these patients suitable candidates for renal transplantation [48].

TOOLS TO EVALUATE RESPONSE

It was often difficult to determine if patients with myeloma or amyloid had achieved a response after transplantation. The presence of renal failure often made it difficult to quantify the urinary loss of monoclonal light chain used to assess response. In addition, patients with amyloid as well as light chain myeloma frequently have no measurable monoclonal protein in the serum. In amyloid patients with associated nephrotic syndrome, the albuminuria made it difficult to estimate absolute quantities of free light chain in the urine. This obstacle to accurate response assessment has been reduced recently by the introduction of the free light chain assay [49, 50]. Now, serum free light chains can be measured, and the ratio between the involved and uninvolved light chains is an excellent correction for the renal insufficiency that results in reduced light chain excretion. Patients with myeloma who have renal insufficiency and nearly all patients with amyloid who do not have a quantifiable monoclonal protein can now be assessed by the nephelometric measurement of free light chain [51].

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REFERENCES

- JEMAL A, TIWARI RC, MURRAY T, et al: Cancer statistics, 2004. *CA Cancer J Clin* 54:8–29, 2004
- KYLE RA, GERTZ MA, WITZIG TE, et al: Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* 78:21–33, 2003
- ALEXANIAN R, BARLOGIE B, DIXON D: Renal failure in multiple myeloma: pathogenesis and prognostic implications. *Arch Intern Med* 150:1693–1695, 1990
- ATTAL M, HAROUSSEAU J-L, STOPPA AM, et al, FOR THE INTERGROUPE FRANÇAIS DU MYÉLOME: A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med* 335:91–97, 1996
- CHILD JA, MORGAN GJ, DAVIES FE, et al: High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med* 348:1875–1883, 2003
- ATTAL M, HAROUSSEAU JL, FACON T, et al: Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med* 349:2495–2502, 2003
- PALUMBO A, BRINGHEN S, PETRUCCI MT, et al: Intermediate-dose melphalan improves survival of myeloma patients aged 50–70: Results of a randomised controlled trial. *Blood* 104:3052–3057, 2004
- REECE DE, BREDESON C, PEREZ WS, et al: Autologous stem cell transplantation in multiple myeloma patients <60 vs. ≥60 years of age. *Bone Marrow Transplant* 32:1135–1143, 2003
- PALUMBO A, BRINGHEN S, BERTOLA A, et al: Multiple myeloma: Comparison of two dose-intensive melphalan regimens (100 vs. 200 mg/m²). *Leukemia* 18:133–138, 2004
- PHILLIPS GL, MEISENBERG B, REECE DE, et al: Amifostine and autologous hematopoietic stem cell support of escalating-dose melphalan: A phase I study. *Biol Blood Marrow Transplant* 10:473–483, 2004
- KERGUERIS MF, MILPIED N, MOREAU P, et al: Pharmacokinetics of high-dose melphalan in adults: Influence of renal function. *Anticancer Res* 14:2379–2382, 1994
- TRICOT G, ALBERTS DS, JOHNSON C, et al: Safety of autotransplants with high-dose melphalan in renal failure: A pharmacokinetic and toxicity study. *Clin Cancer Res* 2:947–952, 1996
- GIRALT S, BENSINGER W, GOODMAN M, et al: ¹⁶⁶Ho-DOTMP plus melphalan followed by peripheral blood stem cell transplantation in patients with multiple myeloma: Results of two phase 1/2 trials. *Blood* 102:2684–2691, 2003
- BREITZ H, WENDT R, STABIN M, et al: Dosimetry of high dose skeletal targeted radiotherapy (STR) with ¹⁶⁶Ho-DOTMP. *Cancer Biother Radiopharm* 18:225–230, 2003
- BALLESTER OF, TUMMALA R, JANSSEN WE, et al: High-dose chemotherapy and autologous peripheral blood stem cell transplantation in patients with multiple myeloma and renal insufficiency. *Bone Marrow Transplant* 20:653–656, 1997
- SAN MIGUEL JF, LAHUERTA JJ, GARCIA-SANZ R, et al: Are myeloma patients with renal failure candidates for autologous stem cell transplantation? *Hematol J* 1:28–36, 2000
- TOSI P, ZAMAGNI E, RONCONI S, et al: Safety of autologous hematopoietic stem cell transplantation in patients with multiple myeloma and chronic renal failure. *Leukemia* 14:1310–1313, 2000
- BADROS A, BARLOGIE B, SIEGEL E, et al: Results of autologous stem cell transplant in multiple myeloma patients with renal failure. *Br J Haematol* 114:822–829, 2001
- BLADÉ J, FERNANDEZ-LLAMA P, BOSCH F, et al: Renal failure in multiple myeloma: Presenting features and predictors of outcome in 94 patients from a single institution. *Arch Intern Med* 158:1889–1893, 1998
- FASSAS A, TRICOT G: Results of high-dose treatment with autologous stem cell support in patients with multiple myeloma. *Semin Hematol* 38:231–242, 2001
- GERTZ M: Transplantation for multiple myeloma: Pertinent questions. *Blood* 102:3472–3475, 2003
- BLADÉ J, VESOLE DH, GERTZ M: High-dose therapy in multiple myeloma. *Blood* 102:3469–3470, 2003
- TAURO S, CLARK FJ, DUNCAN N, et al: Recovery of renal function after autologous stem cell transplantation in myeloma patients with end-stage renal failure. *Bone Marrow Transplant* 30:471–473, 2002
- IMRIE K, ESMAIL R, MEYER RM: The role of high-dose chemotherapy and stem-cell transplantation in patients with multiple myeloma: a practice guideline of the Cancer Care Ontario Practice Guidelines Initiative. *Ann Intern Med* 136:619–629, 2002
- HAHN T, RONDEAU C, SHAIKAT A, et al: Acute renal failure requiring dialysis after allogeneic blood and marrow transplantation identifies very poor prognosis patients. *Bone Marrow Transplant* 32:405–410, 2003
- ROSSI L, CARDARELLI F, VAMPA ML, et al: Membranous glomerulonephritis after haematopoietic cell transplantation for multiple myeloma. *Nephron* 88:260–263, 2001
- REGO F, ALCANTARA P, BUINHO F, et al: Autologous peripheral stem cell transplantation for multiple myeloma in a patient with a 10 year-old kidney transplant: Case report and clinical issues. *Transplant Proc* 35:1102–1104, 2003
- SUN X, PETERSON LC, GONG Y, et al: Post-transplant plasma cell myeloma and polymorphic lymphoproliferative disorder with monoclonal serum protein occurring in solid organ transplant recipients. *Mod Pathol* 17:389–394, 2004
- ZEIER M, PERZ J, LINKE RP, et al: No regression of renal AL amyloid in monoclonal gammopathy after successful autologous blood stem cell transplantation and significant clinical improvement. *Nephrol Dial Transplant* 18:2644–2647, 2003
- VAN GAMEREN II, HAZENBERG BP, JAGER PL, et al: AL amyloidosis treated with induction chemotherapy with VAD followed by high

- dose melphalan and autologous stem cell transplantation. *Amyloid* 9:165–174, 2002
31. GERTZ MA, LACY MQ, DISPENZIERI A, et al: Stem cell transplantation for the management of primary systemic amyloidosis. *Am J Med* 113:549–555, 2002
 32. ZENHAUSERN R, TOBLER A, LEONCINI L, et al: Fatal cardiac arrhythmia after infusion of dimethyl sulfoxide-cryopreserved hematopoietic stem cells in a patient with severe primary cardiac amyloidosis and end-stage renal failure. *Ann Hematol* 79:523–526, 2000
 33. GERTZ MA, LACY MQ, DISPENZIERI A: Immunoglobulin light chain amyloidosis and the kidney. *Kidney Int* 61:1–9, 2002
 34. COMENZO RL, GERTZ MA: Autologous stem cell transplantation for primary systemic amyloidosis. *Blood* 99:4276–4282, 2002
 35. HAYES-LATTIN BM, CURTIN PT, FLEMING WH, et al: Toxic megacolon: A life-threatening complication of high-dose therapy and autologous stem cell transplantation among patients with AL amyloidosis. *Bone Marrow Transplant* 30:279–285, 2002
 36. COMENZO RL: Hematopoietic cell transplantation for primary systemic amyloidosis: What have we learned. *Leuk Lymphoma* 37:245–258, 2000
 37. GERTZ MA, LACY MQ, DISPENZIERI A: Myeloablative chemotherapy with stem cell rescue for the treatment of primary systemic amyloidosis: A status report. *Bone Marrow Transplant* 25:465–470, 2000
 38. LEUNG N, SLEZAK JM, BERGSTRALH EJ, et al: Acute renal insufficiency after high-dose melphalan in patients with primary systemic amyloidosis during stem cell transplantation. *Am J Kidney Dis* 45:102–111, 2005
 39. SNANOUDJ R, MAMZER-BRUNEEL MF, HERMINE O, et al: Recovery of acute renal failure and nephrotic syndrome following autologous stem cell transplantation for primary (AL) amyloidosis. *Nephrol Dial Transplant* 18:2175–2177, 2003
 40. CASSERLY LF, FADIA A, SANCHORAWALA V, et al: High-dose intravenous melphalan with autologous stem cell transplantation in AL amyloidosis-associated end-stage renal disease. *Kidney Int* 63:1051–1057, 2003
 41. BLUM W, KHOURY H, LIN HS, et al: Primary amyloidosis patients with significant organ dysfunction tolerate autologous transplantation after conditioning with single-dose total body irradiation alone: A feasibility study. *Biol Blood Marrow Transplant* 9:397–404, 2003
 42. SHERIF AM, REFAIE AF, SOBH MA, et al: Long-term outcome of live donor kidney transplantation for renal amyloidosis. *Am J Kidney Dis* 42:370–375, 2003
 43. LEUNG N, GRIFFIN MD, DISPENZIERI A, et al: Living donor kidney and autologous stem cell transplantation for primary systemic amyloidosis (AL) with predominant renal involvement. *Am J Transplant* 5:1660–1670, 2005
 44. DISPENZIERI A, LACY MQ, KYLE RA, et al: Eligibility for hematopoietic stem-cell transplantation for primary systemic amyloidosis is a favorable prognostic factor for survival. *J Clin Oncol* 19:3350–3356, 2001
 45. DISPENZIERI A, KYLE RA, LACY MQ, et al: Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: A case-control study. *Blood* 103:3960–3963, 2004
 46. SELDIN DC, ANDERSON JJ, SANCHORAWALA V, et al: Improvement in quality of life of patients with AL amyloidosis treated with high dose melphalan and autologous stem cell transplantation. *Blood* 104:1888–1893, 2004
 47. LEUNG N, LAGER DJ, GERTZ MA, et al: Long-term outcome of renal transplantation in light-chain deposition disease. *Am J Kidney Dis* 43:147–153, 2004
 48. ROYER B, ARNULF B, MARTINEZ F, et al: High dose chemotherapy in light chain or light and heavy chain deposition disease. *Kidney Int* 65:642–648, 2004
 49. MEAD GP, CARR-SMITH HD, DRAYSON MT, et al: Serum free light chains for monitoring multiple myeloma. *Br J Haematol* 126:348–354, 2004
 50. LACHMANN HJ, GALLIMORE R, GILLMORE JD, et al: Outcome in systemic AL amyloidosis in relation to changes in concentration of circulating free immunoglobulin light chains following chemotherapy. *Br J Haematol* 122:78–84, 2003
 51. ABRAHAM RS, KATZMANN JA, CLARK RJ, et al: Quantitative analysis of serum free light chains: A new marker for the diagnostic evaluation of primary systemic amyloidosis. *Am J Clin Pathol* 119:274–278, 2003