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PERSPECTIVES IN BASIC SCIENCE

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 μmol/L, 29% of patients present with a serum creatinine value from 106 to 176 μmol/L, and 19% have a creatinine value greater than 176 μmol/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 μmol/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 μmol/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

[a]Mikhael 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.

[b]Sirohi 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/m^2. Doses as high as 280 mg/m^2 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/m^2 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 ^{166}holmium-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 ^{166}holmium-containing regimens 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