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Autologous Hematopoietic Stem Cell Transplantation May Reverse Renal Failure in Patients with Multiple Myeloma

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Approximately 20% of patients with multiple myeloma (MM) have renal failure at diagnosis, and about 5% are dialysis-dependent. Many of these patients are considered ineligible for autologous hematopoietic stem cell transplantation (auto-HSCT) because of a high risk of treatment-related toxicity. We evaluated the outcome of 46 patient with MM and renal failure, defined as serum creatinine >2 mg/dL sustained for >1 month before the start of preparative regimen. Patients received auto-HSCT at our institution between September 1997 and September 2006. Median serum creatinine and creatinine clearance (CrCl) at auto-HSCT were 2.9 mg/dL (range: 2.0-12.5) and 33 mL/min (range: 8.7-63), respectively. Ten patients (21%) were dialysis-dependent. Median follow-up in surviving patients was 34 months (range: 5-81). Complete (CR) and partial responses (PR) after auto-HSCT were seen in 9 (22%) and 22 (53%) of the 41 evaluable patients, with an overall response rate of 75%. Two patients (4%) died within 100 days of auto-HSCT. Grade 2-4 nonhematologic adverse events were seen in 18 patients (39%) and included cardiac arrythmias, pulmonary edema, and hyperbilirubinemia. Significant improvement in renal function, defined as an increase in flomerular filtration rate (GFR) by 25% above baseline, was seen in 15 patients (32%). Kaplan-Meier estimates of 3-year progression-free survival (PFS) and overall survival (OS) were 36% and 64%, respectively. In conclusion, auto HSCT can be offered to patients with MM and renal failure with acceptable toxicity and with a significant improvement in renal function in approximately one-third of the transplanted patients. In this analysis, a melphalan (Mel) dose of 200 mg/m^2 was not associated with an increase in toxicity or nonrelapse (Mel) mortality (NRM).

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INTRODUCTION

Renal insufficiency is frequently observed in multiple myeloma (MM). Up to 20% of newly diagnosed patients have renal failure, defined as serum creatinine >2 mg/dL [1,2]. Several factors contribute to renal failure in MM patients, including monoclonal light-chain-induced proximal tubular damage, hypercalcemia, dehydration, infection, hyperuricemia, and the use of nephrotoxic drugs [2]. Amyloid deposition and plasma cell infiltration are less frequent causes for renal impairment [3]. Renal failure was a predictor of poor prognosis in early chemotherapy trials for MM. Patients requiring dialysis were reported to have a poorer prognosis [4]. Renal failure is also considered a marker of high tumor burden and inadequate therapy [5].

High-dose chemotherapy (HDT) using melphalan (Mel) 200 mg/m^2 with autologous hematopoietic stem cell transplantation (auto-HSCT) improves the outcome of patients with MM in terms of remission rates and survival with a nonrelapse mortality (NRM) of <5% [6,7]. Because of concerns about higher rates of treatment-related toxicity and NRM, patients with renal insufficiency are frequently excluded from HDT protocols [8]. A few recent reports have addressed the

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role of HDT and auto-HSCT in patients with MM and concurrent renal failure, and showed that this treatment is feasible in patients with renal insufficiency, even in a dialysis-dependent setting [8-10]. The objective of this retrospective analysis study was to evaluate the safety and feasibility of this approach in patients with myeloma and renal failure, who received HDT and auto-HSCT at our institution. We also analyzed the impact of Mel dose on the outcome, and the reversibility of renal failure.

PATIENTS AND METHODS

Patients

Forty-six patients with MM and concomitant renal failure, defined as a serum creatinine ≥2 mg/dL sustained for more than 1 month before the start of preparative regimen HSCT. Patients received high-dose melphalan followed by auto-HSCT were included in this analysis. Patients received auto-HSCT between April 1997 and September 2006. Ten patients (21%) were hemodialysis-dependent. Median age at auto-HSCT was 55 years (range: 29-72). Forty-two patients were <65 years old and 4 were ≥65 years old. Median interval between diagnosis and transplant was 12 months (range: 5-107). All patients gave written informed consent before auto-HSCT, which was obtained in accordance with the Declaration of Helsinki.

Treatment

Peripheral blood stem cells (PBSC) were mobilized and collected following granulocyte colony-stimulating factor (G-CSF) alone (36) or chemotherapy + G-CSF (10) [11]. All 46 patients received high-dose Mel on days −4 and −3. Thirty-three patients received a Mel dose of 200 mg/m^2, 9 patients received 180 mg/m^2, and 4 patients received 140 mg/m^2 [11,12]. Patients with older age or worse renal impairment were not intended to receive a lower Mel dose. Before this analysis, the common practice of some attending physicians was to use a lower mel dose for patients with impaired renal function, a practice that was not uniform and hence the discrepancy in doses. Unmanipulated autologous stem cells were infused 48 hours later. All patients received G-CSF, 5 μg/kg/day from day +1 until the absolute neutrophil count (ANC) was 0.5×10^9/L for 2 consecutive days, in accordance with our departmental guidelines. Blood products were given for hemoglobin ≤8 g/dL and platelets $<20 \times 10^9$/L. Hemodialysis was administered as indicated in dialysis-dependent patients. Mucositis prophylaxis included standard mouth care and prophylactic antimicrobial agents according to standard departmental guidelines. None of the patients receive keratinocyte growth factor (KGF) for mucositis prophylaxis.

Renal Failure

Renal failure was defined as serum creatinine ≥2 mg/dL sustained for >1 month before the start of preparative regimen [8,9,13,14]. The glomerular filtration rate (GFR) was derived from the serum creatinine values by the Cockcroft Gault formula. This formula is considered a Level A recommendation for accurate measurement of renal function [15]. The data on patient's sex, height, and weight at the time of transplant were taken into consideration for baseline GFR calculations. GFR was calculated for each patient at baseline (pretransplant) and at 3, 6, 9, and 12 months after auto-HSCT. Based on the baseline GFR at the initial diagnosis the patients were subgrouped as chronic kidney disease (CKD) stages 3 to 5 (Table 1) according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI initiative) [16].

Improvement in renal function was defined as an increase in GFR by ≥25% compared to the baseline. Patients were also grouped according to dialysis dependency status.

Response Criteria

The european group for Blood and Marrow Transplantation (EBMT) response criteria were used to define complete remission (CR), partial response (PR), and relapse [17]. CR was defined as the absence of original monoclonal protein in urine and serum by immunofixation, <5% plasma cells in marrow aspirate, and no increase in the size or number of lytic bony lesions. Progressive disease (PD) was defined as 1 of the following: (1) >25% increase in serum or urine monoclonal protein, or plasma cells in the bone marrow, or (2) increase in the size or number of lytic bony lesions. All responses were in reference to auto-HSCT.

Table 1. Chronic Kidney Disease Staging*

Stage	Description	GFR, mL/min/1.73 m^2
—†	At increased risk	≥60 (with chronic kidney disease risk factors)
1	Kidney damage: normal or increased GFR	≥90
2	Kidney damage, mild decrease in GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney failure	<15 (or dialysis)

GFR indicates glomerular filtration rate.

*National Kidney Foundation Kidney Disease Outcomes Quality Initiative Classification, Prevalence, and Action Plan for Stages of Chronic Kidney Disease.

†Stages 1 to 5 indicate patients with chronic kidney disease; the first row, without a stage number, indicates patients at increased risk for developing chronic kidney disease.

Chronic kidney disease is defined as either kidney damage or GFR less than 60 mL/min per 1.73 m^2 for 3 or more months.

Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.