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Moderate Renal Function Impairment Does Not Affect Outcomes of Reduced-Intensity Conditioning with Fludarabine and Melphalan for Allogeneic Hematopoietic Stem Cell Transplantation

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Nonrelapse mortality (NRM) after reduced-intensity allogeneic transplants is likely to be influenced by abnormalities in renal function. We studied 141 patients diagnosed with acute myelogenous leukemia (AML) (n = 131) or high-risk myelodysplastic syndrome (MDS) (n = 10) who underwent allogeneic transplantation with fludarabine (Flu)/melphalan (Mel)-based regimens and hypothesized that moderate to mild renal function impairment increases NRM in this setting. Flu dose consisted of 25-30 mg/m^2 for 4 days and Mel dose was 100-180 mg/m^2. Donors were HLA-compatible siblings (n = 69) and matched unrelated donors (n = 72). Disease status at transplantation was complete remission (n = 56, 40%) or active disease (n = 85, 60%). The influence of the estimated glomerular filtration rate (GFR) measured before transplantation on outcomes was analyzed. GFR was estimated by both the Cockcroft-Gault (CG) and the modified diet in renal disease (MDRD) equations, using the creatinine value obtained prior to starting chemotherapy. Evaluated outcomes were overall survival (OS), NRM, and treatment-related mortality (TRM) at day 100 and 1-year posttransplantation. Median age was 55 years (range: 21-74 years); 59% of the patients were male. Estimated GFR by CG was ≥90 for 45 (32%), 60-89 for 78 (55%), and <60 for 18 (13%) patients. When estimated by MDRD, GFR was ≥90 for 65 (46%), 60-89 from 66 (47%), and <60 for 10 (7%) patients. The majority of patients by both estimations had a GFR between 60 and 89 (n = 78 by CG and n = 66 by MDRD) with no difference in the evaluated outcomes between this group and the subgroup of patients with a GFR <60 ($P > .05$). There were no differences in OS and NRM at day 100 and 1-year posttransplantation in the 3 groups by any GFR estimation method. In conclusion, a mild to moderate decrease in GFR was not associated with an increase in NRM.

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INTRODUCTION

Renal injury is a common complication of hematopoietic cell transplantation (HCT), and is associated with increased morbidity and mortality [1,2]. Consequently, impairment of renal function is often used as an exclusion criterion when selecting patients who undergo HCT. Acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) are diseases of the elderly, a population usually with some degree of renal impairment, frequently worsened by previous chemotherapy and exposure to a variety of nephrotoxic drugs.

Nonmyeloablative (NMA) conditioning regimens were developed as less toxic modalities of treatment for the elderly population and those with serious comorbidities who are not eligible for standard myeloablative (MA) HCT [3]. As proposed by Champlin et al. [4,5], the definition of a truly nonablative regimen is one that can be given routinely without stem cell support, with neutrophil recovery within 28 days, and one in which mixed chimerism can be routinely detected early after transplantation. Regimens that cannot be

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safely administered without stem cell support have been termed reduced-intensity conditioning (RIC) [6]. At M.D. Anderson Cancer Center, we use the combination of a purine analog (fludarabine [Flu]) with an alkylating agent (melphalan [Mel]) [3,6-11].

We hypothesized that patients with AML/MDS and renal impairment before the administration of the Flu/Mel regimen would have worse outcomes, including higher nonrelapse mortality (NRM), than those with a normal renal function. The hypothesis was investigated in a homogeneous patient population including only AML/MDS patients that received RIC and allogeneic HCT.

METHODS

Eligibility

Patients were included in this retrospective analysis if they had either AML or high-risk MDS and had undergone an allogeneic HCT from an HLA-compatible donor with an RIC regimen with Flu/Mel. Patients were treated under consecutive protocols, and were eligible to receive Flu/Mel if older than 50 years, or in the presence of clinical comorbidities that precluded the use of myeloablative conditioning. Patients were also selected on the basis of having a creatinine level <1.6 mg/dL. Patients that received a previous allogeneic transplant were excluded. From August 1996 until May 2006, a total of 141 patients met these eligibility criteria and were included in the present analysis.

Reduced-Intensity regimen

All subjects signed written informed consents, and their treatment protocols and this study were approved by our institutional review board (IRB). Patients received Flu 25 to 30 mg/m^2 for 4 to 5 days in combination with melphalan Mel 100, 140, or 180 mg/m^2 total dose. Antithymocyte globulin (ATG) was added for recipients of unrelated (UD) or mismatched related donor HCT. Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus (FK506, Prograf, Fujisawa, Deerfield, IL) and methotrexate (MTX) 5 mg/m^2 i.v. on days 1, 3, 6, and 11 after transplantation for all but 2 patients. Tacrolimus levels were monitored 3 times a week and kept at therapeutic ranges of 5 to 10 ng/dL during the first 100 days and then tapered at the discretion of the primary physician depending on donor type, disease status at time of transplantation, presence or absence of GVHD, and presence of residual donor cells as documented by chimerism or cytogenetic analysis. Tacrolimus target levels and MTX doses were similar regardless of baseline renal function.

Antibacterial, antifungal, and antiviral prophylaxis consisted of trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* prophylaxis, acyclovir or valacyclovir for herpes simplex virus (HSV) prophylaxis, and surveillance cytomegalorivus (CMV) antigenemia testing for all patients with preemptive use of ganciclovir in the event of a positive antigenemia test. All patients received filgrastim (granulocyte colony-stimulating factor [G-CSF]) (Neupogen, Amgen, Thousand Oaks, CA) 5 mg/kg s.c. daily from day +7 until achievement of an absolute neutrophil count (ANC) above 1.5×10^9/L for 3 days. Packed red blood cells were administered to maintain hemoglobin levels greater or equal to 8 g/dL. Platelet transfusions were administered to keep the platelet count at a level of $\geq 10 \times 10^9$/L. All blood products were filtered and irradiated. Donor stem cells or bone marrow (BM) were procured using standard mobilization protocols and pheresis techniques. The stem cells or BM from all related donors were collected at the M.D. Anderson Cancer Center, and they were processed according to current institutional guidelines and protocols. All healthy donors signed written informed consent for the procedure. BM procured from UD was obtained through the National Marrow Donor Program (NMDP) according to applicable guidelines at the time of procurement. As required by the NMDP, donors gave consent at the donor center after an extensive screening and information process.

Renal Function Assessment

Baseline glomerular filtration rate (GFR) was estimated the day prior to the conditioning regimen and in other time points before and after HCT using both the abbreviated modified diet in renal disease (MDRD) equation: GFR (mL/min/1.73 m^2) = $186 \times P_{cr}^{-1.154} \times age^{-0.203} \times (1.212 \text{ if black}) \times (0.742 \text{ if female})$ and the Cockcroft-Gault (CG) equation, GFR (mL/min/1.73 m^2) = $(140 - age) \times (weight)/(P_{Cr} \times 72) \times (0.85 \text{ if female})$, where P_{cr} is the plasma creatinine level [12,13]. Pretransplantation baseline renal function was classified into 5 stages, as suggested by the National Kidney Foundation (NKF) [12], and patients were divided into 3 risk groups according to their GFR: <60 (NKF 3, 4, and 5), 60-89 (NKF 2), ≥90 (NKF 1) mL/min/1.73 m^2.

Statistical Considerations

The primary endpoints were overall survival (OS), NRM, and treatment-related mortality (TRM) on day +100 and 1 year after transplantation. Outcomes were estimated starting on the day of HCT. NRM was defined as death occurring in the absence of progression or relapse of malignancy. TRM was defined as NRM excluding deaths attributed to GVHD [14]. Actuarial OS was estimated by the method of Kaplan-Meier. The cumulative incidence method accounting for competing risks was used to estimate the rates of TRM, NRM, absolute creatinine level above 1.5 mg/dL, and requirement