ASBMT
American Society for Blood and Marrow Transplantation

The Contribution of Malglycemia to Mortality among Allogeneic Hematopoietic Cell Transplant Recipients

Marilyn J. Hammer,[1] Corey Casper,[2,3,4] Ted A. Gooley,[2,5] Paul V. O'Donnell,[2,3] Michael Boeckh,[2,3] Irl B. Hirsch[3]

Allogeneic hematopoietic cell transplantation (HCT) continues to be associated with substantial rates of nonrelapse mortality (NRM). Numerous factors influence glucose metabolism among HCT recipients. We hypothesized that "malglycemia," defined as hyperglycemia, hypoglycemia or increased glycemic variability, is associated with increased mortality in HCT patients. In a retrospective cohort study Cox regression was used to assess the association of malglycemia after transplant with day 200 NRM. A total of 66,062 blood glucose (BG) measurements from 1175 adult allogeneic HCT recipients between 2000 and 2005 at the Fred Hutchinson Cancer Research Center were evaluated (median 0.55 values per patient-day, range: 0.09-3.62). Overall, there were 215 cases of NRM by day 200 post-HCT and 601 deaths from any cause throughout observation. After adjustment for previously identified factors associated with NRM, all 3 components of malglycemia were associated with increased NRM when individually modeled as time-dependent covariates. Specifically, the hazard ratio for death was 1.93 for BG >200 mg/dL ($P = .0009$) and 2.78 for BG >300 ($P = .0004$) compared with BG 101-150 mg/dL. A minimum BG ≤89 was associated with a risk of day 200 NRM 2.17 times that of a minimum BG >89 ($P < .0001$). The upper quartile of glucose variability was associated with a 14.57-fold increase in risk of NRM by day 200 relative to the first quartile ($P < .0001$). These retrospective data indicate that malglycemia is associated with mortality following HCT. The applicability of these findings to other situations and whether correcting malglycemia in HCT can lead to reductions in mortality remain to be determined.

Biol Blood Marrow Transplant 15: 344-351 (2009)

KEY WORDS: Hyperglycemia, Hypoglycemia, Glycemic variability, Hematopoietic cell transplant, Infection, Mortality

INTRODUCTION

Disordered glucose metabolism is associated with increased risk of death among persons with both chronic and acute medical illnesses [1-3]. Recently, efforts have been made to control hyperglycemia during inpatient hospitalization, but results from clinical trials and retrospective analyses have demonstrated inconsistent findings with intensive insulin therapy [2-4]. The first prospective, randomized control trial in critically ill surgery patients reported a 42% reduction in mortality [2], but these results were not replicated in the same group's second study of critically ill medical patients [5]. Other populations studied in randomized control trials including those with acute myocardial infarction [6,7], and more recently severe sepsis [8], have not shown improvements with intensive insulin therapy. Conversely, other retrospective data have suggested benefits from improved glucose control in the hospital [9,10].

There is also growing evidence that hypoglycemia may have a profound detrimental effect on outcomes, including death and length of stay, thus limiting the efforts for meticulous glucose control in the hospital [11]. Besides the known neuroglycopenic dangers of seizures and coma, the data suggest that rates of "severe hypoglycemia" (often defined in this literature as a blood glucose less than 40 mg/dL) approximate 18% in a research setting [5,8]. Whether this is a marker of

From the [1]Department of Biobehavioral Nursing & Health Systems, University of Washington, Seattle, Washington; [2]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington; [3]Department of Medicine, University of Washington, Seattle, Washington; [4]Department of Epidemiology, University of Washington, Seattle, Washington; and [5]Department of Biostatistics, University of Washington, Seattle, Washington.

The first 2 authors contributed equally to this work.

Financial disclosure: See Acknowledgments on page 350.

Correspondence and reprint requests: Irl B. Hirsch, M.D., Department of Medicine, University of Washington Medical Center-Roosevelt, 4225 Roosevelt Way NE, Suite 101, Box 354691, Seattle, WA 98105 (e-mail: ihirsch@u.washington.edu).

Received October 7, 2008; accepted December 8, 2008
1083-8791/09/153-0001$36.00/0
doi:10.1016/j.bbmt.2008.12.488

poor outcome or offsets any benefit from intensive insulin therapy is unknown.

Glycemic variability, a measurement of glucose instability, was recently shown to be a predictor of mortality in critically ill patients [12]. There has also been increased interest in evaluating the impact of glycemic variability on the vascular outcomes of diabetes [13]. It appears that oxidative stress is generated by variable glucose levels [14] but at this time the role of this process in the pathogenesis of micro- and macroangiopathy is unclear.

Despite impressive gains in the safety of HCT over the last 20 years, nonrelapse mortality (NRM) remains high. Major causes of NRM include infection, organ toxicity, and graft-versus-host disease (GVHD). Under the best of circumstances, NRM occurs in 10% to 15% of HCT patients by 100 days and in 20% to 30% of patients by 2 to 3 years [15,16], and it is therefore important to identify modifiable factors that could further reduce NRM. In contrast to critically ill patient groups, little data exist regarding the relative contribution of the components of malglycemia, which we define as disordered glucose metabolism consisting of hyperglycemia, hypoglycemia, or increased glycemic variability, to infections or mortality posttransplant.

Allogeneic HCT provides a novel setting in which to examine the association between malglycemia and outcome, as the population consists of patients who are of closely monitored and expected to have a high incidence of hyperglycemia, infections, and mortality posttransplant. In this retrospective study, we examined the association between disordered glucose metabolism and the post-HCT outcomes of infection and death among a cohort of 1175 patients who underwent allogeneic HCT at a single transplant center.

METHODS

Patients

All patients 18 years of age and older undergoing allogeneic HCT at the Fred Hutchinson Cancer Research Center (FHCRC), Seattle, Washington, were approached for participation in a study protocol that allows for retrospective review of medical records; $>$ 90% of patients gave their consent. All patients who consented and were undergoing their first HCT between 2000 and 2005 who had $\geq$1 glucose measurement between day 0 (time of receipt of stem cells) and day 100 were included. This study received approval by the FHCRC institutional review board.

Evaluation and Outcomes

Data including basic demographic characteristics, details of HCT, and any available measurements of blood glucose (BG, serum or plasma) level were abstracted from the FHCRC HCT database. Bedside capillary glucose values were not used in this analysis. Serum and plasma glucose concentrations were determined using the central laboratory's Beckman-Coulter Synchron LX-20 automated chemistry analyzer. Information on infections was obtained from 3 sources. All bacteremias were identified through electronic records from the microbiology laboratory. Data on cytomegalovirus reactivation and disease [17], invasive fungal infections [18] and Gram-negative bacteremias [19] were obtained through previously validated databases.

Statistical Analysis

Cox regression was used to assess the association between BG and outcome following HCT. Five glycemic parameters were examined: individual BG values, glycemic variability (measured by the standard deviation of individual BG values), average BG value, minimum BG value, and maximum BG value. BG values between days 0 and 100 following HCT were considered, as this is a time period during which regular BG measurements are taken because of the fact that patients remain in the FHCRC system and are closely monitored during this time window. Outcomes included day 200 nonrelapse mortality (NRM), overall mortality (OM), and fungal infection, cytomegalovirus (CMV) disease, and Gram-negative infections by day 130 post-HCT. Day 130 was chosen to allow a 30-day incubation period for infection acquired by day 100. For infections that could occur multiple times in a given patient, an Andersen-Gill model was fit [20]. Unless otherwise specified, all models were adjusted for severity of disease (low, intermediate, and high) [21], patient age at HCT, type of donor (HLA-identical sibling versus alternate donors [unrelated, mismatched sibling, or nonsibling relative]), year of transplant, and presence of grades 2-4 graft-versus-host disease [22] (GVHD, modeled as a time-dependent covariate). We consider GVHD (a post-HCT factor) because its occurrence is associated with increased NRM, and GVHD is treated with steroids, which increases BG. Each glycemic parameter was treated as a time-dependent covariate and modeled as a continuous variable using a cubic spline with 5 knots set (prior to data analysis) at the 5th, 25th, 50th, 75th, and 95th percentiles [23]. Ninety-five percent confidence intervals for the point estimates of hazard ratios were estimated from the observed variance/covariance matrix. In addition, each parameter was modeled as a categoric variable. All reported *P*-values are 2-sided. Those comparing nested regression models were derived from the likelihood-ratio test (LRT), and *P*-values from regression models were estimated from the Wald test. No adjustments were made for multiple comparisons.