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The Impact of Pretransplant Hypoalbuminemia on Survival in patients With Leukemia Who Underwent Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT): A Nutritional Problem?

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ABSTRACT

Objective. Serum albumin level is considered to be a marker reflecting the nutritional status in both healthy subjects and patients with malignancies. In this study we sought to investigate the association between pretransplantation serum albumin levels and prognosis among patients with leukemia who underwent allogeneic hematopoietic stem cell transplantation (alloHSCT).

Methods. We retrospectively analyzed the data of 102 patients who underwent alloHSCT from 2004 to 2010. Pretransplant serum albumin, D-dimer, creatinine, and fibrinogen levels drawn within 10 days before transplantation were obtained from patient files. All parameters were divided into 2 groups: normal levels (group 1) versus abnormal levels (group 2). Our normal range of serum albumin is 3.2–5.2 g/dL; patients with pretransplantation albumin level ≥3.2 g/dL were included in group 1 versus group 2 with <3.2 g/dL.

Results. The patients included 42 (41.1%) female and 60 (58.9%) male patients. The diagnoses were acute myeloblastic leukemia in 65 (63.7%) and acute lymphoblastic leukemia in 37 (36.3%). The median age was 26.0 years (range, 13–57). Univariate and multivariate analysis showed that patients with serum albumin levels <3.2 g/dL experienced significantly lower overall survival (OS) compared with ≥3.2 g/dL (hazard ratio [HR] 2.32 [range, 1.23–4.54] and HR 2.70 [range 1.38–5.26], respectively; $P = .009$). The median (range) OS in group 2 was 230.0 (184.0–544.0) days versus 570.5 (249.5–1,101.0) days in group 1 ($P = .007$). For disease free survival (DFS) evaluation, univariate and multivariate analysis showed that patients with serum albumin levels <3.2 g/dL had significantly lower values compared with patients with serum albumin ≥3.2 g/dL. (HR 2.17 [range 0.98–4.76] and HR 2.85 [range, 1.25–6.66], respectively; $P = .046$). The median (range) DFS in group 2 was 184.0 (61.0-524.0) days versus 445.0 (199.0–917.5) days in group 1 ($P = .045$). Among the patient characteristics the presence of infection was a significant independent variable for worse OS (HR 2.12 [range, 0.98–4.36], $P = .036$). The other parameters—age, sex, donor status, time to transplant interval, conditioning regimens, HLA status, and number of total infused $CD34^+$ cells—showed no significant effect on OS and DFS ($P = .05$).

Conclusions. Pretransplantation decreased serum albumin levels were associated with poor survival in patients with leukemia who underwent alloHSCT.

ALLOGENEIC HEMATOPOIETIC stem cell transplantation (allo-HSCT) is considered to be a curative treatment for various hematologic malignancies. Some data regarding specific pretransplantation comorbidity indices can be used to select appropriate candidates for allo-HSCT.[1,2] Although improvement of outcomes has been achieved in recent decades via advances in many

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procedures, such as the prevention of graft-versus-host disease (GVHD), infectious complications remain an important contributor to transplant-related mortality.[3,4] The prognostic value of hypoalbuminemia as a determinant for post-transplantation outcomes remains unclear. Hypoalbuminemia is a strong predictor of poor clinical outcomes among patients with cardiac failure[5] and end-stage renal disease (ESRD)[6,7] as well as elderly patients requiring chronic hospitalization.[8,9] Some data have provide significance of serum parameters, such as fibrinogen,[10] D-dimer,[11] and creatinine,[12] for prognosis among allo-HSCT recipients. In the present study, we analyzed the prognostic significance of hypoalbuminemia before transplantation with other clinical and laboratory variables in 102 patients with acute leukemia who underwent allo-HSCT.

PATIENTS AND METHODS

In this retrospective study, we analyzed the data from 102 patients with leukemia who underwent allo-HSCT from April 2004 to June 2010. The data were obtained from patient records, including values of serum albumin, D-dimer, fibrinogen, and creatinine drawn within 10 days before transplantation. The patients were divided into 2 groups: normal levels for each parameter (group 1) and abnormal levels (group 2). Patients with a pretransplantation serum albumin level <3.2 g/dL were included in group 2 and those with albumin level ≥3.2 g/dL in group 1. Myeloablative (MA) conditioning regimens (used in 88 patients [86.2%]) mostly consisted of busulfan (Bu) plus cyclophosphamide (Cy) and Cy plus total body irradiation (TBI). The cytogenetic data for risk evaluation were recorded from patient archives in the Department of Medical Genetics. Platelet engraftment, was defined as the day on which platelet count exceeded 20,000/mm^3; neutrophil engraftment when >500/mm^3 for ≥3 days consecutively. The study was approved by our Ethics Committee.

Statistical Analysis

Shapiro-Wilk test was used and histogram q-q plots constructed to check the normality of data distribution. To compare differences between groups, chi-square analysis was used for categoric and Mann-Whitney *U* test for continuous variables. Values are expressed as frequency and percentage or median and interquartile range (IQR). Kaplan-Meier method was used to estimate survival probability, and log-rank test for comparisons. Also, univariate and multivariate Cox proportional hazards regression was used to determine the most significant independent factors. Significant variables at $P < .15$ on univariate analysis were need in a multivariate model with backward stepwise selection using the Wald statistic at $P < .10$ stringency level, seeking to identify independent risk factors. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were also calculated. Analyses were performed with the use of SPSS Statistics 20.0 (IBM-SPSS, Chicago, Illinois).

RESULTS

We enrolled 102 patients previously diagnosed with acute leukemia who underwent allo-HSCT, including 42 (41.1%) female and 60 (58.9%) male. The diagnoses were acute myeloblastic leukemia (AML) (n = 65; 63.7%) and acute lymphoblastic leukemia (ALL) (n = 37; 36.3%). The overall median age was 26.0 years (IQR 13.0–57.0). The most common conditioning regimens were, Bu/Cy (n = 67; 65.7%), TBI/Cy (n = 13; 12.7%), and Flu/Cy (n = 7; 6.9%). Peripheral blood stem cells were used as the allogeneic graft source in all patients. For risk classification; 42 patients (41.1%) were defined as high versus 60 (58.9%) low risk. Whereas 75 patients (73.5%) underwent allo-HSCT in the first 12 months after the diagnosis of leukemia (<12 mo), 27 (26.5%) underwent allo-HSCT after completion of the first 12 months following the diagnosis.

Engraftment

The median day for platelet engraftment was 11 days (IQR: 8–27) in group 1 and 12 days (IQR, 7–30) in group 2 ($P = .286$). The median day for neutrophil engraftment was 14 days (IQR, 8–36) in group 1 and 13 days (IQR, 9–32) in group 2 ($P = .782$). In general estimation, serum albumin levels had no effect on either platelet or neutrophil engraftment days.

Hypoalbuminemia and Outcomes: Overall Survival

The median overall survival (OS) in group 2 was 230.0 (IQR, 184.0–544.0) days versus 570.5 (IQR, 249.5–1101.0) days in group 1. Our analyses indicated OS to be significantly poorer among patients with a low serum albumin level (<3.2 g/dL) before transplantation. Univariate and multivariate analysis showed that patients with a serum albumin level <3.2 g/dL displayed significantly lower OS compared with those whose value was ≥3.2 g/dL (HR 2.32, 95% CI 1.23–4.54; and HR 2.70, 95% CI 1.38–5.26; respectively; $P = .009$). A greater risk of death was observed among ALL vs AML patients (HR 2.71, 95% CI 1.45–5.08; $P = .008$). However, laboratory evaluation for serum parameters showed pretransplantation serum fibrin degradation product (D-dimer), fibrinogen, and creatinine levels to excrt no significant effect on OS (HR 1.47, 95% CI 0.55–3.84, [$P = .435$]; HR 1.17, 95% CI 0.57–2.41, [$P = .651$]; HR 1.06, 95% CI 0.14–7.76 [$P = .95$]; respectively). Patients were analyzed for cytogenetic risk [t(9,22), nucleophosmin (NPM) mutation, FLT3-ITD], chemoresistance to chemotherapy, and relapsed disease. Univariate and multivariate analysis showed that patients with high risk displayed significantly lower OS compared with low-risk subjects (univariate analysis: HR 2.51, 95% CI 1.36–4.63, multivariate analysis: HR 2.78, 95% CI 1.50–5.15; $P = .003$). Among patient characteristics; the presence of infection was a significant independent variable predictive of worse OS (HR 2.12, 95% CI 0.98–4.36; $P = .036$). The parameters of age, sex, donor status, time to transplant interval, sex match, conditioning regimens, HLA status, and number of total infused CD34$^+$ cells showed no significant effect on OS ($P < .05$).

Hypoalbuminemia and Outcomes: Disease-Free Survival

The median disease-free survival (DFS) for group 2 was 184.0 (IQR, 61.0–524.0) days versus 445.0 (IQR,