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Nonfluorodeoxyglucose-Avid Persistent Splenomegaly at Time of Transplantation Delays Neutrophil and Platelets Engraftment without Affecting Survival in Patients with Lymphomas Undergoing Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

It is unclear if persistent splenomegaly in the presence of a negative positron emission tomography (PET) scan before allogeneic hematopoietic cell transplantation (HCT) influences post-transplantation outcomes in patients with lymphoma. We retrospectively reviewed records of 152 patients who underwent allogeneic HCT for various lymphomas. Centralized review of pretransplantation computed tomography (CT) and PET images was performed. Spleen volume (SV) was measured using the freehand volume segmentation tool in AW Workstation software (General Electric, Waukesha, WI). Splenic index (SI) was calculated as a product of width, thickness, and length of the spleen. Normal SV was defined as SV < 314.5 cm^3 and normal SI was defined as SI ≤ 480 cm^3, as described in the literature. Among the study population, 42.8% received an allogeneic HCT from an HLA-matched related donor, 36.2% from a matched unrelated donor, 12.5% from a mismatched unrelated donor, and 8.6% received a double umbilical cord blood transplantation. Most (61.8%) received myeloablative conditioning. Median age at transplantation was 52 (range, 21 to 68) years. Pre–allogeneic HCT spleen CT and PET images were available on 88% and 70.3% patients, respectively. SV ranged from 90 cm^3 to 4684 cm^3 with a median of 290.5 cm^3 and a mean of 400.3 cm^3. SI calculation showed a range from 50.3 cm^3 to 8276.4 cm^3 with a median of 582.1 cm^3 and a mean of 771.2 cm^3. The majority of patients (83.1%) had PET-negative spleen before allogeneic transplantation. Engraftment was delayed in PET-negative patients with persistent splenomegaly, with median days to neutrophil engraftment of 17 versus 16 ($P = .03$) and median days to platelet engraftment of 16 versus 14 ($P = .04$) when using SV. However, persistent splenomegaly did not appear to impact progression-free survival ($P = .11$) or overall survival ($P = .37$). Splenomegaly in the setting of a PET-negative study before allogeneic HCT delays neutrophil and platelet engraftment but does not appear to affect survival. Future studies using registry data or larger multicenter studies would be required to evaluate the impact of splenomegaly and its fluorodeoxyglucose avidity on allogeneic HCT outcomes in specific subtypes of lymphomas.

INTRODUCTION

In the United States, currently over 5000 hematopoietic cell transplantations (HCT) are performed every year for the treatment of lymphomas, with a ratio of autologous to allogeneic (allo) HCT of about 4:1 [1]. Splenomegaly is a common clinical feature in lymphomas and the incidence of splenomegaly is as high as 45% in certain lymphomas [2].

Engraftment of neutrophils and platelets after allo-HCT can be a key determinant of early morbidity and mortality, as prolonged cytopenias are associated with increased risk of severe infections and bleeding [3]. Several studies have shown that splenomegaly may have a role in delaying

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engraftment in patients who receive an allo-HCT for myeloid malignancies [3,4]. Helenglass et al. showed delayed engraftment in patients with chronic myeloid leukemia with splenomegaly undergoing allo-HCT [3]. Recently, Akpek et al. reported a Center for International Blood and Marrow Research study on 9683 patients who underwent myeloablative allo-HCT between 1990 and 2006 for chronic myeloid leukemia, myeloproliferative disorders including myelofibrosis, and myelodysplastic syndrome, and concluded that splenomegaly before allo-HCT resulted in delayed engraftment whereas splenectomy before allografting appeared to facilitate hematopoietic engraftment without affecting survival [4]. However, it is unclear whether persistent splenomegaly before allo-HCT would have an impact in post-transplantation relapse or survival outcomes in patients with lymphomas.

The role of positron emission tomography (PET) imaging in diagnosis and prognosis of splenic masses and lymphoma has been fully validated and it has now become an integral part of the standard response criteria for lymphomas [5-8]. Also, a recent analysis by Center for International Blood and Marrow Research showed that pretransplantation PET scan predicts disease relapse but does not predict survival after allogeneic transplantation [9]. To our knowledge, there are no published studies examining the impact of persistent splenomegaly in the setting of PET negativity in patients undergoing allo-HCT for lymphomas.

Accordingly, we conducted a retrospective study to evaluate the significance of persistent splenomegaly (along with splenic fluorodeoxyglucose [FDG] avidity) and its effect on transplantation outcomes in lymphoid malignancies in patients who received allo-HCT.

METHODS

Data Source and Study Design

Data were obtained on consecutive adult (age ≥18) patients who received an allo-HCT for lymphomas between January 1, 2008 and December 31, 2013 at the Moffitt Cancer Center. Prior autologous transplantation was not an exclusion criterion. Additionally, pretransplantation computed tomography (CT) and PET images of all patients performed during vital organ testing within 2 months before allo-HCT were reviewed by 1 radiologist to maintain operator-dependent uniformity in measurements. Spleen volume (SV) was measured using the freehand volume segmentation tool in AW Workstation software (General Electric, Waukesha, WI) on CT images. Splenic index (SI) was calculated as a product of width, thickness, and length of the spleen. *Normal SV* and *normal SI* were defined as SV < 314.5 cm^3 and SI ≤ 480 cm^3, respectively, as described in the literature [10,11]. Spleen and liver mean standardized uptake value (SUV)s were calculated to document splenic FDG avidity using region-of-interest measurements over the spleen and liver with standard radiology techniques. Spleens with mean SUV of lower value than liver were considered *negative*.

This observational research was conducted in compliance with all the applicable federal regulations regarding the protection of research participants as assessed by the institutional review board and in compliance with the Declaration of Helsinki.

Study Endpoints and Outcomes Definitions

The primary endpoint of this study was to determine if persistent splenomegaly in the setting of PET-negative staging at time of allo-HCT affects progression-free (PFS) and overall survival (OS) in patients with lymphomas. *PFS* was defined as time elapsed between allografting and relapse or disease progression. *OS* was calculated from day of transplantation until death from any cause.

Secondary endpoints included neutrophil engraftment, platelet engraftment, cumulative incidence of nonrelapse mortality (NRM), and relapse. *Neutrophil engraftment* was defined as the first day of achieving sustained absolute neutrophil count (ANC) greater than 500 × 10^6/L for 3 consecutive days after transplantation. *Platelet engraftment* was defined as the first day of achieving a continued platelet count of 20 × 10^9/L without transfusion support. *NRM* was defined as death from any cause without relapse of underlying lymphoma, and *relapse* was defined as lymphoma recurrence after transplantation by standard imaging and/or morphologic criteria.

Statistical Analysis

Medians, means, and ranges were tabulated for continuous variables and percentages were calculated for categorical demographic variables. Patient-, disease-, and transplantation-related variables of interest were tabulated. The log-rank test and Kaplan-Meier product limit estimate for time-to-event variables, as well as (semi-) parametric approaches (eg, Cox proportional hazards regression models) were used as appropriate to study the potential clinical effects of these variables on outcomes and hazard ratios (HRs) and their 95% confidence intervals (CIs) are reported when feasible.

Time to neutrophil and platelet engraftment was described as median days to event and using cumulative incidence estimates, patients in whom the count nadir was never below the defined criteria (ANC <500 x 10^6/L and platelet <20 × 10^9/L) were not evaluable for engraftment endpoint. Death was used as a competing risk. Statistical analysis was performed with StataCorp. 2013 (Stata Statistical Software: Release 13. College Station, TX: StatCorp LP).

RESULTS

A total of 152 consecutive patients who underwent an allo-HCT met the study eligibility. Of these, 134 (88%) patients had pre-HCT CT images and 107 (70.3%) had pre-HCT PET images available for review and were included for further stratified outcome analysis based on spleen status as shown in Tables 1 and 2.

Overall Outcomes in All Patients (n = 152)

Survival

Two-year PFS and OS were 62.5% (95% CI, 53.3% to 70.4%) and 57.3% (95% CI, 48.9% to 64.8%), respectively, for all patients as shown in Figure 1.

Engraftment kinetics

Neutrophil engraftment occurred at a median of 16 days (range, 7 to 43 days) and platelet engraftment at a median of 16 days (range, 9 to 145 days).

Graft-versus-host disease and NRM

The cumulative incidence of 100-day grades II to IV acute graft-versus-host disease was 66.4% (95% CI, 57.6% to 74.6%) whereas 2-year cumulative incidence of moderate-to-severe chronic graft-versus-host disease was 70.2% (95% CI, 60.9% to 78.6%). NRM was 22.6% (95% CI, 16.3% to 29.6%) at 2 years.

Disease relapse

Cumulative incidence of disease relapse at 2 years was 26.1% (95% CI, 19.4% to 33.5%).

Outcomes Based on Spleen Assessment by Volume or Index (n = 134)

Based on the available imaging data, 46.3% patients met the criteria for splenomegaly by volume (SV ≥ 314.5 cm^3) and 59.7% by SI (> 480 cm^3), respectively.

Splenomegaly by SV

Survival. The 2-year PFS and OS for patients with SV ≥ 314.5 cm^3 were 58.9% (95% CI, 44.3% to 71.1%) and 57.6% (95% CI, 44.2% to 68.8%), respectively, whereas for patients with SV < 314.5 cm^3, PFS and OS were 68.9% (95% CI, 55.2% to 79.1%) and 58.1% (95% CI, 45.8% to 68.5%), respectively, without significant differences in either PFS (HR, 1.20; 95% CI, .66 to 2.18; $P = .55$) or OS (HR, 1.06; 95% CI, .64 to 1.75; $P = .83$) (Figure 2).

Engraftment. Median days to neutrophil engraftment in patients with SV < 314.5 cm^3 and SV ≥ 314.5 were 16 versus