Major Article

Ocular complications in a young pediatric population following bone marrow transplantation

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PURPOSE To investigate ocular complications associated with bone marrow transplant and associated continued maintenance therapy in a preschool population.

METHODS The medical records of patients <7 years of age were reviewed retrospectively. Patient charts were screened for cataract formation, dry eye, and other anterior and posterior segment disease.

RESULTS Of 270 cases reviewed, 91 met inclusion criteria. Mean age at diagnosis was 3.17 years. Average follow-up was 5.8 years (range, 1.9 months–14.1 years). Of the 91, 37 patients developed cataracts (35 bilaterally) over a 14-year period. Cumulative incidence corrected for competing event (death before cataract) for the study population was found to be 58.4% after 14 years. Univariate analysis for cataract formation showed statistical significance for total body irradiation dose, age at diagnosis, race, donor type (related vs unrelated), product type, diagnosis type, survival status, calcineurin inhibitor use, and bisulfan, cytarabine, and thiotepa use. Multivariate analysis for competing event (death), showed that total body irradiation dose was not statistically significant; however, when studied in a binary logistic regression model, total body irradiation dose was statistically significant. Notably, steroid use and presence of graft-versus-host disease did not show statistical significance for cataract development. No other ocular complication was found in sufficient quantities to allow statistical analyses.

CONCLUSIONS Due to the high incidence of cataract formation in this population, especially those enduring a treatment regimen with total body irradiation, we propose screening examinations by a pediatric or general ophthalmologist at least annually. We also urge a low threshold for treatment of dry eye syndrome. (J AAPOS 2018;■:1-5)

Allogeneic bone marrow transplantation (BMT) has become a widely used treatment for childhood leukemia, myelodysplastic syndrome, lymphoma, solid tumors, and several nonmalignant diseases.[1] Ocular complications following BMT include cataract development and dry eye syndrome. The effects of these ocular complications on patients' quality of life can be significant, especially in children, who are less likely to report symptoms. Young children who have not reached school age are especially vulnerable, because they often have limited verbal skills and may not be able to express their symptoms, and they may not respond to any therapeutic interventions. In addition, young children who become long-term survivors may have to endure these complications for many years.

Most of the published reports describing ocular complications in children following BMT are retrospective and include children of all ages.[1,2] Studies include both allogeneic and autologous recipients.[1,2] The present study aimed to analyze the incidence and risk factors for ocular complications following allogeneic BMT in children ≤6 years of age at the time of transplantation.

Subjects and Methods

This study was approved by the Institutional Review Board of St. Jude Children's Research Hospital and was compliant with the US Health Insurance Portability and Accountability Act of

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1996. The medical records of consecutive patients ≤6 years of age who received allogeneic BMT at St. Jude Children's Research Hospital between 1995 and 2010 were reviewed retrospectively. Patients were included if they had ophthalmic examinations prior to BMT and at least one follow-up examination during the 5 years after transplantation.

Ocular examinations were performed by an ophthalmologist at St. Jude. Examination included visual acuity when permitted by age, biomicroscopic or penlight examination of the anterior segment, and dilated fundus examination. All patients included in the study underwent transplantation according to the treatment protocols used by the Bone Marrow Transplant Department at St. Jude. Pretransplant conditioning regimens were determined by the patients' diagnoses and treatment protocols.

The patient's medical records were screened for development of cataract and dry eye as well as any additional ocular disease as described in the ophthalmologist's examination notes. The following data were collected: patient demographics, diagnosis and treatment protocol, age at transplantation, dose of radiation received (total and dose per fraction), site of irradiation, history of irradiation prior to conditioning therapy, use of calcineurin inhibitors for any reason, chemotherapy used for conditioning, inclusion of steroids in conditioning regimen, presence of acute and chronic graft-versus-host disease (GVHD), pre- and post-transplant ophthalmic examinations, post-transplant ocular complications, post-transplant ocular complaints, and treatment outcomes.

Statistical Analysis

Descriptive statistics were analyzed and compared either by the Pearson χ^2 test or the Fisher exact test for categorical variables, and by a two-sample t test or a Wilcoxon rank sum test for quantitative variables based on the normality assumption criteria, respectively. Logistic regression was performed using the ocular complication as binary outcomes, and its association with all other covariates was studied. Overall survival probabilities were estimated using the Kaplan-Meier method and compared using log-rank test. Overall survival was defined as the time from BMT until death from any cause, censoring those alive at the last follow-up. The cumulative incidence of an event was estimated by the Kalbfleisch-Prentice method, and compared using Gray's test.[3,4] In the estimation of cumulative incidence of development of cataract, deaths due to any cause is considered a competing event. Fine and Gray's regression model was used to evaluate the associations between cumulative incidence and all other covariates listed below. Risk factors considered in univariate analysis included age at transplant, sex, race, presence or absence of cytomegalovirus, diagnosis, dose of radiation received, donor type, site of irradiation, history of irradiation prior to conditioning therapy, treatment, conditioning regimen, inclusion of steroids in conditioning regimen, product type, presence of acute and chronic GVHD, and type of treatment.

The parameters associated with outcomes in univariate analyses at a nominal level of $P = 0.15$ were included in their respective multivariate analyses based on a stepwise model selection strategy that used logistic regression and Fine and Gray's regression model. All the reported P values are two-sided and considered significant if <0.05. Statistical analyses were performed with *SAS* version 9.4 and *R* version 2.13.1.

Results

A total of 270 young children received allogeneic BMT during the study period. Of these, 91 (41 females) met inclusion criteria; 179 patients were excluded because of either a lack of pre-BMT evaluation (33) or lack of follow-up, including 83 that died before they were seen twice in the eye clinic. Sixty-eight patients were white, 13 were African American, and 10 were of other ethnic origins. All patients included in our study received allogeneic BMT. The mean patient age at time of BMT was 3.2 years (range, 0.1-6.99 years). Mean follow-up period was 5.8 years (range, 1.9 months to 14.1 years); median follow-up was 5.25 years. Fourteen of the patients ultimately died during the follow-up period from disease complications.

The most common indications for BMT were acute lymphoblastic leukemia (26 patients) and acute myelogenous leukemia (18 patients). Other indications for BMT are noted in eTable 1; eTable 2 lists characteristics of the study population.

Seventy-two eyes of 37 patients (41%) patients developed cataracts following BMT; cataracts were bilateral except in all but 2 patients. Of these 37 patients, 8 required cataract surgery. After surgery, 5 patients achieved visual acuities of 20/20 to 20/30; 2 achieved 20/40; and 1 achieved 20/80. Descriptive analysis showed the following variables as significant for development of cataract ($P < 0.05$): older age at diagnosis, unmatched donor, product type (hemopoetic progenitor cells–marrow), match, survival status, treatment, specific chemotherapy used for conditioning treatment (busulfan, cytrabine, and thiotepa), total body irradiation (TBI) dose, and use of calcineurin inhibitors. Additionally, white race and diagnosis met the threshold for inclusion in the multivariate analyses ($P < 0.15$).

Some underlying disease processes were also associated with higher prevalence of cataract development. For instance, cataract was more likely in patients with hematologic malignancies than in patients with nonhematologic malignancies ($P = 0.06$).

Three particular chemotherapy agents showed statistical significance in the univariate logistic model: busulfan ($P = 0.002$) and thiotepa ($P = 0.02$) were associated with a decreased incidence of cataract formation, whereas cytarabine ($P < 0.0001$) was associated with increased incidence. Busulfan and TBI were the only factors that showed statistical significance in the multivariate analysis (Table 1). The odds ratio of cataract development in a patient treated with busulfan was 0.14 (95% CI, 0.04-0.75).

Survival was a factor in cataract development; therefore, a life table was created to show the increased incidence of cataract development with increasing survival (Figure 1). The cumulative incidence of cataract development