Avascular Necrosis of Bone after Allogeneic Hematopoietic Cell Transplantation in Children and Adolescents

Xiaxin Li [1], Ruta Brazauskas [2], Zhiwei Wang [3], Amal Al-Seraihy [4], K. Scott Baker [5], Jean-Yves Cahn [6], Haydar A. Frangoul [7], James L. Gajewski [8], Gregory A. Hale [9], Jack W. Hsu [10], Rammurti T. Kamble [11], Hillard M. Lazarus [12], David I. Marks [13], Richard T. Maziarz [8], Bipin N. Savani [7], Ami J. Shah [14], Nirali Shah [15], Mohamed L. Sorror [5,16], William A. Wood [17], Navneet S. Majhail [18,19,*]

[1] *Banner Children's Specialists Pediatric Hematology/Oncology, Banner Health, Mesa, Arizona*
[2] *Division of Biostatistics, Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin*
[3] *Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin*
[4] *Hematopoietic Stem Cell Transplantation Program, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia*
[5] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[6] *Clinique Universitaire d'Hematologie, University Hospital, Grenoble, France*
[7] *Pediatric Blood and Marrow Transplant Program, Vanderbilt University Medical Center, Nashville, Tennessee*
[8] *Bone Marrow & Stem Cell Transplant Program, Oregon Health and Science University, Portland, Oregon*
[9] *Division of Hematology and Oncology, All Children's Hospital, St. Petersburg, Florida*
[10] *Division of Hematology & Oncology, Shands HealthCare and University of Florida, Gainesville, Florida*
[11] *Section of Hematology-Oncology, Baylor College of Medicine Center for Cell and Gene Therapy, Houston, Texas*
[12] *Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, Ohio*
[13] *BMT Unit, Bristol Children's Hospital, Bristol, United Kingdom*
[14] *Division of Hematology/Oncology, Department of Pediatrics, Mattel Children's Hospital at UCLA, Los Angeles, California*
[15] *National Cancer Institute, National Institutes of Health, Bethesda, Maryland*
[16] *Division of Medical Oncology, Department of Medicine, University of Washington School of Medicine, Seattle, Washington*
[17] *Division of Hematology and Oncology, University of North Carolina Hospitals, Chapel Hill, North Carolina*
[18] *Center for International Blood and Marrow Transplant Research, Minneapolis, Minnesota*
[19] *Blood & Marrow Transplant Program, Cleveland Clinic, Cleveland, Ohio*

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A B S T R A C T

We conducted a nested case-control study within a cohort of 6244 patients to assess risk factors for avascular necrosis (AVN) of bone in children and adolescents after allogeneic transplantation. Eligible patients were ≤21 years of age, received their first allogeneic transplant between 1990 and 2008 in the United States, and had survived ≥ 6 months from transplantation. Overall, 160 patients with AVN and 478 control subjects matched by year of transplant, length of follow-up and transplant center were identified. Patients and control subjects were confirmed via central review of radiology, pathology, and/or surgical procedure reports. Median time from transplant to diagnosis of AVN was 14 months. On conditional logistic regression, increasing age at transplant (≥5 years), female gender, and chronic graft-versus-host disease (GVHD) were significantly associated with increased risks of AVN. Compared with patients receiving myeloablative regimens for malignant diseases, lower risks of AVN were seen in patients with nonmalignant diseases and those who had received reduced-intensity conditioning regimens for malignant diseases. Children at high risk for AVN include those within the age group where rapid bone growth occurs as well as those who experience exposure to myeloablative conditioning regimens and immunosuppression after hematopoietic cell transplantation for the treatment of GVHD. More research is needed to determine whether screening strategies specifically for patients at high risk for developing AVN with early interventions may mitigate the morbidity associated with this complication.

INTRODUCTION

Avascular necrosis (AVN) of the bone is a debilitating late complication of allogeneic hematopoietic cell transplantation (HCT) that can be associated with significant morbidity [1,2]. The incidence and risk factors for AVN have been well described in adult transplant recipients with an estimated cumulative incidence of 3% to 10% at 5 years after transplantation [1,3-9]. Graft-versus-host disease (GVHD), exposure to corticosteroids or calcineurin inhibitors, cumulative dose of corticosteroids, older age, female gender, and use of total body irradiation (TBI) as part of conditioning regimen have been identified as risk factors for AVN in adult HCT recipients. Although its pathogenesis is poorly understood, potential mechanisms for development of AVN include local vascular damage that leads to increased marrow edema and ischemia, ineffective osteoblastic repair processes due to metabolic factors, and mechanical stresses [1,10].

Large studies specifically focusing on evaluating risk factors for AVN in pediatric HCT survivors are lacking. Factors such as immaturity and ongoing growth of bones and endocrine dysfunction related to growth and sex hormones

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* Correspondence and reprint requests: Navneet S. Majhail, MD, MS, Blood & Marrow Transplant Program, Cleveland Clinic, 9500 Euclid Ave., R35, Cleveland, OH 44195.
E-mail address: ksandhya@stanford.edu (S. Kharbanda).

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are exclusive to children and may modulate the risks of AVN in a different way from adults. Hence, extrapolating findings from studies that have only included adults or have combined adults with children can be a challenge. Also, it is not known whether the relatively recent less toxic preparative regimens (nonmyeloablative and reduced-intensity conditioning) are associated with lower risks of AVN than conventional myeloablative regimens in this population. To better understand the risk factors for AVN after allogeneic HCT in children and adolescents, we conducted a case-control study using data from the Center for International Blood and Marrow Transplant Research (CIBMTR). We evaluated risk factors from both "older approaches" (myeloablative regimens, greater use of sibling donors) and "contemporary approaches" (nonmyeloablative/reduced intensity regimens, greater use of unrelated donors) in our analysis.

METHODS

Data Source

The CIBMTR is a working group of more than 450 transplantation centers worldwide that contribute detailed data on HCTs to a Statistical Center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program in Minneapolis. Participating centers are required to report all transplants consecutively, and patients are followed longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and onsite audits of participating centers ensure data quality. Data are collected before transplant, 100 days and 6 months after transplant, and annually thereafter, or until death. The follow-up research forms specifically inquire whether a recipient has developed AVN post-transplantation. Observational studies conducted by the CIBMTR are performed under the guidance of the Institutional Review Board of the National Marrow Donor Program and are in compliance with all applicable federal regulations pertaining to the protection of human research participants.

Patients

For our study, we selected first allogeneic HCT recipients aged $\leq$ 21 years at transplantation who had been reported to the CIBMTR between 1990 and 2008. Because screening and management practices for AVN can vary by region, we restricted our cohort to patients who had received their transplant at a center in the United States. We also limited our cohort to patients who had survived at least 6 months or more after transplantation because our analysis was focused on long-term HCT survivors and on transplant-related risk factors for AVN. Patients with any diagnosis and recipients of both myeloablative and reduced-intensity/nonmyeloablative regimens were eligible.

Selection of Patients and Control Subjects

Overall, 6244 patients met study eligibility criteria and were the basis for selection of patients and control subjects for our study. Patients were those who had a diagnosis of AVN reported on post-transplant follow-up. AVN of any joint was considered. For all cases identified as potential patients, we requested diagnostic and/or treatment information from centers to ascertain the diagnosis of AVN (eg, copies of radiologic investigations, pathology reports, or surgical operative notes). We excluded 2 patients from our analysis for whom we were not able to confirm the diagnosis of AVN from their transplant center.

We established a pool of control subjects using eligible patients who had received their transplant at the same centers as patients and did not have a diagnosis of AVN reported to the CIBMTR. For each patient we chose a control subject that was matched by year of transplantation ($\pm$1 year) and follow-up duration (follow-up post-transplant no less than the interval from HCT to onset of AVN for the corresponding patient). Control subjects were selected from the same center as patients, if available. If a control subject could not be identified for a patient from the same center, control subjects were selected from another center that had patients with AVN included in this study.

Each patient was matched with up to 3 control subjects. For patients with several matched control subjects, 3 were selected randomly for the analysis. For each selected control subject, we contacted transplant centers and requested them to review medical records and confirm that the patient did not have AVN. On this review, 4 control subjects were identified to have AVN post-transplantation and were subsequently considered as patients. Control subjects were excluded from the analysis if they had a pre-HCT diagnosis of AVN (n = 1) or if centers were not able to confirm the absence of AVN diagnosis (n = 26).

We identified 160 confirmed patients with AVN and 478 matched control subjects. Among these case-control pairs, 407 (85%) were matched within the same center as the patient. One hundred fifty nine patients had 3 matched control subjects, and 1 patient had 1 matched control subject.

Study Definitions and Statistical Analysis

Conditioning regimens were defined as myeloablative, reduced intensity, and nonmyeloablative using established guidelines [11]. Because no clear guidelines exist for classifying conditioning regimens for nonmalignant diseases, these diseases were considered as a separate category when describing conditioning regimen intensity. Disease status for malignant diseases was assigned as early, intermediate, or advanced [12]. Early disease included acute myeloid leukemia or acute lymphoblastic leukemia in first complete remission, chronic myeloid leukemia in first chronic phase, myelodysplastic syndrome refractory anemia, or refractory anemia with ringed sideroblasts or unspecified myelodysplastic syndrome with <5% marrow blasts. Patients with acute myeloid leukemia or acute lymphoblastic leukemia in second or greater remission, chronic myeloid leukemia in second or greater chronic phase, or chronic myeloid leukemia in accelerated phase were classified as intermediate-risk disease. All other patients, including patients with lymphoma, were classified as advanced disease. The National Marrow Donor Program's classification of HLA matching status was used for unrelated donor transplant recipients (well matched, partially matched, or mismatched) [13].

The goal of our case-control study was to assess potential risk factors for developing AVN in children and adolescents after allogeneic HCT. For comparing characteristics between patients and control subjects, we used the chi-square or Fisher's test (as applicable) for categorical variables and Wilcoxon 2-sample test for continuous variables. To evaluate risk factors, we performed multivariable analyses using conditional logistic regression on all matched sets. The following variables were considered in this analysis: age at transplantation, gender, diagnosis, disease status, conditioning regimen intensity, dose of TBI, donor source, and history of GVHD before AVN. If feasible, categories with a small number of patients were combined with related categories. Patients receiving transplant from HLA-mismatched related donors (n = 23), patients with unknown conditioning regimen intensity (n = 2), and patients with unknown date of GVHD onset (n = 14) were excluded from the risk factor analysis.

All *P*-values are 2-sided. All analyses were carried out using SAS statistical software (SAS Institute Inc., Cary, NC).

RESULTS

Characteristics of Patients and Control Subjects

Table 1 shows the characteristics of the 160 AVN patients and 478 control subjects. The median age at transplantation was 15 years for patients and 8 years for control subjects. The primary diagnosis of nonmalignant disorder was higher in the control group (32%) compared with AVN patients (13%). A greater proportion of AVN patients had received TBI containing myeloablative regimen compared with control subjects (65% versus 48%). Related, unrelated, and umbilical cord blood donors were used in 21%, 64%, and 16% of AVN patients and 11%, 69%, and 21% of control subjects, respectively. Fifty-six percent of patients had a history of chronic GVHD before the onset of AVN compared with 49% in the control group.

Among AVN patients, the median time from HCT to the onset of AVN was 14 months (range, <1 to 172 months). In 37% of patients AVN occurred within 1 year of HCT, in 59% AVN occurred 1 to 5 years after HCT, and in 4% it occurred more than 5 years after transplantation. Detailed information was available for 59 patients to completely characterize the extent of joint involvement by AVN. Among these patients, collectively 119 joints were affected by AVN with a median of 2 joints (range, 1 to 6). Femoral head (82%) was the most common site of involvement and was followed by the knee joint (78%), the vertebral column (12%), and the ankle joint (10%). AVN of the shoulder joint was rare (5% of patients). Pathologic fracture was the initial presentation of AVN in 3 patients.

We also evaluated the characteristics of patients included in our study by donor source (related = 83 patients [41% patients, 59% control subjects], unrelated = 432 patients [23% patients, 77% control subjects], umbilical cord blood = 123 [20% patients, 80% control subjects]). There were notable differences among related, unrelated, and umbilical