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Risk Factors for Subsequent Central Nervous System Tumors in Pediatric Allogeneic Hematopoietic Cell Transplant: A Study from the Center for International Blood and Marrow Transplant Research (CIBMTR)

Melissa Gabriel [1], Bronwen E. Shaw [2,*], Ruta Brazauskas [2,3], Min Chen [2], David A. Margolis [4], Henrik Sengelov [5], Ann Dahlberg [6], Ibrahim A. Ahmed [7], David Delgado [8], Hillard M. Lazarus [9], Brenda Gibson [10], Kasiani C. Myers [11], Rammurti T. Kamble [12], Aly Abdel-Mageed [13], Chi-Kong Li [14], Mary E.D. Flowers [15], Minoo Battiwalla [16], Bipin N. Savani [17], Navneet Majhail [18], Peter J. Shaw [1]

[1] *The Children's Hospital at Westmead, Westmeand, New South Wales, Australia*
[2] *CIBMTR (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin*
[3] *Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, Wisconsin*
[4] *Children's Hospital of Wisconsin, Milwaukee, Wisconsin*
[5] *University Hospital, Copenhagen, Denmark*
[6] *Fred Hutchinson Cancer Research Center, Seattle, Washington*
[7] *Department of Hematology Oncology and Bone Marrow Transplantation, The Children's Mercy Hospitals and Clinics, Kansas City, Missouri*
[8] *Indiana University Hospital/Riley Hospital for Children, Indianapolis, Indiana*
[9] *Seidman Cancer Center, University Hospitals Cleveland Medical Center, Cleveland, Ohio*
[10] *Schiehallion Day Care Unit, Royal Hospital for Sick Children, NHS Greater Glasgow and Clyde, Glasgow, United Kingdom*
[11] *Division of Bone Marrow Transplant and Immune Deficiency, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio*
[12] *Division of Hematology and Oncology, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, Texas*
[13] *Helen DeVos Children's Hospital at Spectrum Health, Grand Rapids, Michigan*
[14] *Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong*
[15] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[16] *Hematology Branch, National Heart, Lung and Blood Institute, Bethesda, Maryland*
[17] *Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee*
[18] *Blood & Marrow Transplant Program, Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio*

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A B S T R A C T

Survivors of hematopoietic cell transplantation (HCT) are at risk of subsequent solid tumors, including central nervous system (CNS) tumors. The risk of CNS tumors after HCT in pediatric HCT recipients is not known. We evaluated the incidence and risk factors for CNS tumors in pediatric recipients of allogeneic HCT reported to the Center for International Blood and Marrow Transplant Research between 1976 and 2008. A case control design was used. There were no CNS tumors in the nonmalignant cohort (n = 4543) or in those undergoing HCT for solid tumors (n = 26). There were 59 CNS tumors in 8720 patients transplanted for hematologic malignancies. In comparison with the general population, pediatric HCT recipients with hematologic malignancies had a 33 times higher than expected rate of CNS tumors (95% confidence interval, 22.98 to 45.77; $P < .0001$). The cumulative incidence of subsequent CNS tumors was 1.29% (95% confidence interval .87 to 1.87) at 20 years after HCT. Significant risk factors in the entire cohort were having an unrelated donor (HR, 3.35; $P = .0002$) and CNS disease before HCT for both acute lymphoblastic leukemia (HR, 8.21; $P = .0003$) and acute myeloid leukemia (HR, 6.21; $P = .0174$). Analysis of the matched cohort showed having an unrelated donor transplant (HR, 4.79; $P = .0037$), CNS disease before HCT (HR, 7.67; $P = .0064$), and radiotherapy exposure before conditioning (HR, 3.7; $P = .0234$)

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* Correspondence and reprint requests: Bronwen E. Shaw, MBChB, PhD, CIBMTR/Froedtert & the Medical College of Wisconsin, 9200 W. Wisconsin Ave., Suite C5500, Milwaukee, WI 53226.
E-mail address: beshaw@mcw.edu (B.E. Shaw).

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to be significant risk factors. Chronic graft-versus-host disease was associated with a lower risk (HR, .29; $P = .0143$). Survivors of HCT for nonmalignant diseases did not show an increased incidence of CNS tumors, whereas survivors of hematologic malignancies have a markedly increased incidence of CNS tumors that warrants lifelong surveillance.

INTRODUCTION

Advances in treatment and supportive care have led to increasing numbers of long-term survivors after hematopoietic cell transplantation (HCT) in childhood. Cure, however, has not come without a cost, with survivors at significant risk of a number of long-term complications. Studies have documented that survivors of HCT have increased rates of solid cancers compared with the general population and that this risk increases over time [1-10]. Previous work from the Center for International Blood and Marrow Transplant Research (CIBMTR) has shown that risk factors include total body irradiation (TBI) and young age at HCT [5,10,11]. In 1 study most second solid cancers of the central nervous system (CNS) occurred in children [5]. The risks seem to be highest in those aged < 10 years at the time of HCT, with studies showing 36 to 60 times higher risk of developing subsequent neoplasms [2,5,10,11].

Majhail et al. [12] analyzed the risks of subsequent neoplasms in HCT patients who received busulfan-cyclophosphamide (Bu-Cy) conditioning. In this study of patients with leukemia (acute myeloid leukemia [AML] in first complete remission or chronic myeloid leukemia in first chronic phase [CP1]), none had received previous radiotherapy. This study showed that compared with the general population, patients who had received a Bu-Cy–conditioned HCT had 1.4 times higher than expected rates of invasive solid cancers. An increased risk of CNS tumors was also demonstrated (observed/expected ratio, 3.76; 95% confidence interval, 1.02 to 9.62), with the caveat that this was based on only 4 events. Bu-Cy and other chemotherapy-only conditioning regimens are widely used in the pediatric population, particularly for nonmalignant conditions, so it is important to confirm and quantify this possibly increased risk of CNS tumors.

There are few studies looking at the risks of subsequent neoplasms in pediatric HCT recipients. The largest study examining the development of new malignancies after transplantation for childhood leukemia was published by Socié et al. [10] on behalf of the CIBMTR in 2000. They found an increased risk of solid cancers in this group of patients. Risk factors for solid tumor development were high-dose TBI and younger age at HCT. Brain and thyroid cancers accounted for more than half of the secondary solid cancers in this study. A large study by Curtis et al. [5] also showed that over half of the excess solid tumors in the youngest age group were cancers of the thyroid and brain.

The role of CNS radiotherapy before HCT as a risk factor for secondary CNS tumors is an important one, as cranial irradiation for acute lymphoblastic leukemia (ALL) has also been associated with an increased risk of CNS tumors [13-18]. Whether additional radiotherapy before conditioning adds to the risk of developing secondary CNS tumors after HCT has not previously been studied. There were 9 brain tumors among the 25 solid cancers in the Socié et al. study [10]. Six of these 9 patients had received CNS irradiation before bone marrow transplantation. In the Curtis et al. study there were 13 cases of thyroid (4) and CNS (9) tumors; of these, 9 had received previous cranial radiotherapy [5].

There is little in the published literature looking specifically at the risk of developing CNS tumors in pediatric HCT survivors. Therefore, this current study aimed to determine the incidence and risk factors for developing CNS tumors in survivors of pediatric allogeneic HCT compared with the general population and in particular the role of radiotherapy exposure before conditioning therapy.

METHODS

Data Sources

The CIBMTR is a working group of more than 500 transplantation centers worldwide that contribute detailed data on HCT to a statistical center at the Medical College of Wisconsin. Participating centers are required to report all transplantations consecutively, and compliance is monitored by onsite audits. Computerized checks for discrepancies, physicians' review of submitted data, and onsite audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. The Medical College of Wisconsin and the National Marrow Donor Program institutional review boards approved this study.

The CIBMTR collects data at 2 levels: Transplant Essential Data (TED) and Comprehensive Report Form (CRF) data. TED include disease type, age, gender, pre-HCT disease stage and chemotherapy responsiveness, date of diagnosis, graft type, conditioning regimen, post-transplant disease progression and survival, development of a new malignancy, and cause of death. All CIBMTR centers contribute TED. More detailed disease and pre- and post-transplant clinical information are collected on a subset of registered patients selected for CRF data by a weighted randomization scheme. TED- and CRF-level data are collected pretransplant, day 100, 6 months post-HCT, and annually thereafter or until death. Data for the current analysis were retrieved from CIBMTR (TED and CRF) report forms.

Patients

The initial study population included all patients aged < 21 years old reported to the CIBMTR who received an allogeneic HCT for all disease indications between 1976 and 2008. Among those who met our study criteria, there were no cases of new CNS tumors in patients with nonmalignant disease (n = 4543), transplanted for a solid tumor (n = 26), or receiving nonmyeloablative or reduced-intensity conditioning (n = 161). We therefore excluded these patients from further analysis. In addition, patients were required to have come from centers with a 5-year follow-up completeness index of >80%, survived at least 1 year post-transplant for inclusion, and only CNS malignancies diagnosed at >1 year post transplant were considered. Hence, the final study cohort consisted of 8720 patients with hematologic malignancies who had survived for 1 year or more after HCT.

For each case of subsequent CNS tumor we went back to the reporting center to obtain a pathology report, which was reviewed. Analysis of the risk factors associated with the development of CNS tumors was performed on the entire cohort of patients. The CIBMTR collects limited data on exposure to pretransplant radiation therapy but does not ask for details of the radiation dose and treatment area. Because 1 objective of our study was to evaluate the association of pre-HCT radiation exposure and CNS tumor risk, we conducted a nested case-control study where centers were requested to provide additional information using supplemental data collection forms on all cases with CNS tumors and a subset of patient who served as control subjects. Cases (those with a CNS tumor) identified from the cohort were each matched on disease and duration of follow-up with 2 control subjects drawn from patients transplanted in the population who did not report a CNS tumor. Control subjects were drawn from centers who had reported at least 1 case of new CNS malignancy. Further detailed information was obtained including prior radiotherapy exposure (radiotherapy field, dose and fractionation [cranial, craniospinal], age at radiotherapy, indication, and timing of radiotherapy).

Statistical Analysis

The primary objective of this study was to determine the cumulative incidence of subsequent CNS tumors in allogeneic HCT survivors. Risk factors for subsequent CNS tumors using the entire cohort were analyzed with the