CLINICAL RESEARCH

Corticosteroid Dose as a Risk Factor for Avascular Necrosis of the Bone after Hematopoietic Cell Transplantation

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Exposure to corticosteroids increases the risks of avascular necrosis (AVN) of the bone after hematopoietic cell transplantation (HCT). However, whether this effect is dependent on the dose of corticosteroids is not well known. We conducted a case-controlled study, which included 74 recipients of autologous or allogeneic HCT with AVN and 147 controls without AVN that were matched by age, sex, and year of HCT to cases. Cases with AVN included 8 autologous HCT recipients, 58 myeloablative allogeneic HCT recipients, and 8 recipients of nonmyeloabalative allogeneic HCT. Corticosteroid exposure was expressed as cumulative doses of prednisone. Cases received higher cumulative doses of prednisone than controls, and among allogeneic HCT recipients, cases were more likely to have developed acute and chronic graft-versus-host disease (aGVHD, cGVHD). Cumulative dose of prednisone was an independent risk factor for AVN. Compared to no corticosteroid exposure, exposure to <3870 mg cumulative dose of prednisone was associated with 4.0 (95% confidence intervals, 1.5-11.2) times higher risk, 3870-9735 mg with 5.6 (2.1-15.2) times higher risk and >9735 with 8.6 (3.2-23.5) times higher risk of AVN. Exposure to higher doses of corticosteroids increases the risk of AVN in HCT recipients.

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INTRODUCTION

Improvements in transplantation techniques and supportive care have led to an increasing number of hematopoietic cell transplant (HCT) survivors. These survivors are at risk of late complications because of HCT-related exposures including conditioning-regimen chemotherapy and irradiation, immunosuppressive drugs, and graft-versus-host disease (GVHD) [1-6]. Avascular necrosis (AVN) of the bone is 1 such late complication that occurs because of disruption of blood supply to the bone with resultant death of the bone and collapse of bone structure. AVN has been described in 4% to 19% of HCT survivors and can lead to joint pain, bone destruction, and loss of function with significant impairment in quality of life [7-14]. Up to 48% of affected patients require joint replacement surgery [8,9,11].

Putative risk factors for posttransplant AVN include female sex, older age, allogeneic donor source, acute and chronic GVHD (aGVHD, cGVHD), corticosteroid therapy, and total body irradiation (TBI) [7-9,11,13,15-17]. Recently, exposure to calcineurin inhibitors and mycophenolate mofetil have been implicated as risk factors for development of AVN [13]. The effect of corticosteroid dose on AVN risk has not been previously described. We conducted a single institution case-controlled study to determine the association between cumulative doses of corticosteroids and risk of AVN. We also describe the clinical presentation of AVN in our patient cohort and examine other important risk factors for post-HCT AVN.

METHODS

Patients

The University of Minnesota Blood and Marrow Transplant program's database, which prospectively

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collects transplant and disease-related data and tracks post-HCT outcomes, was queried for AVN of the bone as a post-HCT complication. Patients were eligible for our study if they had received an allogeneic or autologous HCT between 1990 and 2007. All age groups, diagnoses, and donor sources were considered for our study. Medical charts of patients with AVN were reviewed to obtain more information about AVN diagnosis, risk factors, and treatment. To be classified as an AVN case, patients were required to have computed tomography (CT) or magnetic resonance imaging (MRI) evidence of AVN or had undergone joint arthroplasty or another surgical procedure for AVN.

Eighty-four cases of AVN were reported among 3786 patients (autologous = 1157, allogeneic = 2629). From these, 10 patients were excluded; 6 patients did not meet our case definition for AVN (lack of radiological evidence of AVN) and the diagnosis of AVN preceded HCT in 4 patients. Hence, our final cohort of cases consisted of 74 patients (Table 1).

Controls

Two controls were randomly selected for each case from the same cohort of 3786 patients and were matched to cases by age (±5 years), sex, and year of transplantation (±1 year). We did not match cases and controls by transplant type because we wanted to evaluate this variable as a risk factor for AVN. Medical records of controls were reviewed to ascertain absence of AVN or other bone complications. In addition, controls with any documented history of bone and joint related symptoms were excluded.

Risk Factors

The primary objective of this study was to evaluate cumulative dose of corticosteroids as a risk factor for AVN. The following additional risk factors for AVN were also considered a priori: (1) diagnosis (acute leukemia versus chronic myelogenous leukemia versus lymphoma versus nonmalignant disorders), (2) transplant type (autologous versus allogeneic), (3) TBI use (yes versus no), and (4) history of previous transplantation.

Corticosteroid dose was abstracted from a detailed review of medical charts for both cases and controls. For the purposes of this study, corticosteroid dose is presented as prednisone dose in "mg." Dose of other corticosteroids, if used, was converted to an equivalent dose of prednisone. Data on corticosteroid exposure was obtained from the date of diagnosis of hematologic disorder to the date of onset of AVN. Hence, these included use of corticosteroids as part of initial or salvage therapy for the underlying hematologic disorder (eg, prednisone in CHOP chemotherapy regimen for non-Hodgkin lymphomas). For controls, similar data was collected from the time of diagnosis. However, the duration of corticosteroid exposure for controls was considered from the date of transplantation to the date of onset of AVN in its corresponding matched case. Because data on dose of corticosteroids was recorded retrospectively, assumptions about dose were made where there were gaps between reports of corticosteroid use (eg, in between follow-up visits). If the dose on follow-up visit was unchanged, then the dose during the gap was assumed to be the same. If the dose on follow-up visit was lower or higher than previous reported dose, medical records were reviewed for information about a dose taper or increase schedule, which was then used to estimate the corticosteroid dose during that time period.

We could not evaluate duration of corticosteroid exposure as a risk factor for AVN because this was highly correlated with cumulative corticosteroid dose. Similarly, aGVHD and cGVHD were closely

Table 1. Characteristics of Cases and Controls

Characteristic	Cases	Controls	*P*-Value
N	74	147	
Age, years			—*
Median (range)	28 (4-60)	28 (4-60)	
Sex			—*
Male	46 (62%)	95 (64%)	
Female	28 (38%)	52 (36%)	
Diagnosis			.12
Acute leukemia	36 (49%)	49 (33%)	
Chronic myelogenous leukemia	15 (20%)	30 (20%)	
Lymphoma	12 (16%)	32 (22%)	
Nonmalignant disorder	8 (11%)	18 (12%)	
Other	3 (4%)	18 (12%)	
Previous transplant	0	11 (8%)	.02
Transplant type			.04
Allogeneic myeloablative	58 (78%)	93 (63%)	
Allogeneic nonmyeloablative	8 (11%)	17 (12%)	
Autologous	8 (11%)	37 (25%)	
Total-body irradiation dose			.62
No total-body irradiation	15 (20%)	38 (26%)	
200 cGy	8 (11%)	17 (12%)	
1320 cGy	51 (69%)	92 (62%)	
Acute GVHD (allogeneic HCT only)			<.01
No	14 (21%)	49 (44%)	
Yes	52 (79%)	61 (56%)	
Chronic GVHD (allogeneic HCT only)			<.01
No	17 (26%)	73 (66%)	
Yes	49 (74%)	37 (34%)	
Prednisone cumulative dose, mg†			.05
Median (interquartile range)	7043 (2352-12,755)	1800 (0-7895)	
Prednisone cumulative dose, mg†,‡			<.01
No prednisone exposure	6 (8%)	50 (34%)	
<3,870	18 (24%)	37 (25%)	
3,870-9,735	22 (30%)	33 (23%)	
>9,735	28 (38%)	27 (18%)	

GVHD indicates graft-versus-host disease; HCT, hematopoietic cell transplantation.

*Cases and controls were matched by age, sex, and year of transplantation.

†Prednisone equivalent dose of other corticosteroids.

‡Cumulative prednisone dose for cases and controls categorized by tertiles.