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Late Effects in Survivors of Hodgkin and Non-Hodgkin Lymphoma Treated with Autologous Hematopoietic Cell Transplantation: A Report from the Bone Marrow Transplant Survivor Study

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ABSTRACT

We determined the prevalence of self-reported late-effects in survivors of autologous hematopoietic cell transplantation (HCT) for Hodgkin lymphoma (HL, n = 92) and non-Hodgkin lymphoma (NHL, n = 184) using a 255-item questionnaire and compared them to 319 sibling controls in the Bone Marrow Transplant Survivor Study. Median age at HCT was 39 years (range: 13-69) and median posttransplant follow-up was 6 years (range: 2-17). Median age at survey was 46 years (range: 21-73) for survivors and 44 years (range: 19-79) for siblings. Compared to siblings, HCT survivors reported a significantly higher frequency of cataracts, dry mouth, hypothyroidism, bone impairments (osteoporosis and avascular necrosis), congestive heart failure, exercise-induced shortness of breath, neurosensory impairments, inability to attend work or school, and poor overall health. Compared to those receiving no total-body irradiation (TBI), patients treated with TBI-based conditioning had higher risks of cataracts (odds-ratio [OR] 4.9, 95% confidence interval [CI] 1.5-15.5) and dry mouth (OR 3.4, 95% CI 1.1-10.4). Females had a greater likelihood of reporting osteoporosis (OR 8.7, 95% CI: 1.8-41.7), congestive heart failure (OR 4.3, 95% CI 1.1-17.2), and abnormal balance, tremor, or weakness (OR 2.4, 95% CI 1.0-5.5). HL and NHL survivors of autologous HCT have a high prevalence of long-term health-related complications and require continued monitoring for late effects of transplantation.

KEY WORDS

Autologous hematopoietic cell transplantation • Hodgkin lymphoma • Non-Hodgkin lymphoma • Late complications

INTRODUCTION

Autologous hematopoietic cell transplantation (HCT) is standard therapy for patients with aggressive or advanced Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), and can lead to durable long-term remissions. Although autologous HCT is associated with low rates of early transplant-related morbidity and mortality (TRM), the high-dose chemotherapy and total-body irradiation (TBI) used as part of conditioning regimens can potentially increase the risk of late complications of therapy. Lymphoma survivors treated with autologous HCT are at a significantly higher risk for premature death compared to the general population [1], and for developing secondary solid tumors, leukemia, and myelodysplastic syndrome (MDS) [1-6]. However, the incidence and risk factors for nonmalignant late effects in lymphoma autologous HCT survivors have not been systematically investigated.

The current analysis from the Bone Marrow Transplant Survivor Study (BMT-SS) was conducted to describe the prevalence of, and predictors for, a broad spectrum of medical late complications, functional impairments, and overall general health in survivors of HL and NHL treated with autologous HCT.

METHODS

Subjects

The BMT-SS is a collaborative retrospective cohort study established in 2000 between the City of Hope National Medical Center and University of Minnesota to examine the long-term outcomes of HCT survivors. The present report from the BMT-SS was restricted to subjects who met the following eligibility criteria: (1) autologous HCT for HL or NHL between January 1, 1974, and December 31, 1998; (2) age 18 years or older at the time of survey; and (3) survival of at least 2 years from HCT. The analysis compared late effects of transplant in 276 survivors of autologous HCT for lymphoma (HL = 92, NHL = 184) with a sample of 319 siblings. For comparison purposes, a group of siblings was enrolled into the study by assembling a random sample of study participants stratified on the basis of diagnosis, age, sex, and ethnic background, asking these participants to recruit their siblings into the study; and then asking the siblings to complete the same questionnaire as the participants [7]. The comparative evaluations for this analysis were not limited to siblings of HL or NHL participants, but included siblings of all patients who were enrolled in the study and had completed a study questionnaire. The study protocol was reviewed and approved by the Human Subjects Research Review Committee of the participating institutions and all subjects provided informed consent prior to participation in the study.

Data Collection

Participants completed the BMT-SS questionnaire, a 255-item survey assessing medical late effects, current medical conditions, medication use, health status, health behaviors, pregnancy history, demographic characteristics, socioeconomic indicators, insurance coverage, and other information. The BMT-SS questionnaire also asks participants to report impairment of organ systems, limitations that interfere with daily function and the impact of these impairments, and/or functional limitations on daily life either at home, school, or work. The questionnaire was originally developed for use by the Childhood Cancer Survivor Study [8], and was subsequently modified to address topics specifically related to the HCT survivor population. The questionnaire has a yes/no/don't know format for the majority of questions or a Likert scale [9] or ordinal response to score degree of impairment or dysfunction. The BMT-SS questionnaire was validated on a sample of 100 HCT survivors, and the agreement with medical records was excellent (percentage agreement adjusted for chance, kappa >0.8) for musculoskeletal, cardiovascular, pulmonary, and endocrine impairments, and moderate (kappa 0.4-0.7) for second cancers, central nervous system disorders, and eye problems [10]. Data on therapeutic exposures were abstracted from databases at the 2 participating institutions that prospectively collect HCT-related information.

Data Analysis

The prevalence of medical late effects was calculated by tabulating the yes responses to specific questions in the BMT-SS questionnaire. Descriptive statistics including means, medians, standard deviations, frequencies, and ranges were calculated for demographic variables for the sibling comparison group and for demographic and treatment variables for participating and nonparticipating HCT survivors. Two sample *t*-test, chi-square test, or Fisher's exact test, as appropriate, were used to compare differences between survivors and siblings and between lymphoma types among survivors.

Frequencies and percentages were calculated for medical late effects among siblings and HCT survivors as totals and by lymphoma type (HL versus NHL). The prevalence of each medical late effect, after adjusting for age at survey and sex, was compared between cases and siblings by calculating odds ratios and 95% confidence intervals using generalized estimating equations (GEE) with a binomial distribution and a logit link. GEE methods were used in all models to account for the possible correlation between survivors and siblings from the same family [11]. In an analysis limited to survivors only, sex, lymphoma type, and the use of TBI were evaluated in relation to the outcome variables in unconditional logistic regression models. These 3 variables were adjusted for each other in the models with further adjustment for age at transplant and age at survey. Race/ethnicity, stem cell source (peripheral blood versus bone marrow), and institution were not identified as independent predictors of the outcomes, nor did they appreciably alter the estimates, so they were not included in the final models. SAS version 9.1 was used for all analyses (SAS Institute, Cary, NC).

RESULTS

Study Participants

A total of 425 patients with HL or NHL met the eligibility criteria. Of these, 34 (8%) were lost to

Table 1. *Demographic and Treatment Characteristics*

Characteristics	Siblings	Hodgkin's Lymphoma		Non-Hodgkin's Lymphoma	
	N (%)	N (%)	*P*-Value*	N (%)	*P*-Value†
Number	319 (100)	92 (100)		184 (100)	
Median age at survey, years	44	40	<.01	51	<.01
Range, years	19-79	22-63		23-73	
Sex			<.01		<.01
Female	203 (64)	41 (45)		81 (44)	
Male	116 (36)	51 (55)		103 (56)	
Race/ethnicity			.04		.31
White	296 (93)	79 (86)		166 (90)	
Non-White	23 (7)	13 (14)		18 (10)	
Median age at HCT, years	NA	32		44	
Range, years		13-54		17-69	
Median time since HCT, years	NA	6		6	
Range, years		2-17		2-17	
Stem cell source					
BM	NA	22 (24)		34 (18)	
PBSC	NA	54 (59)		128 (70)	
BM and PBSC	NA	16 (17)		22 (12)	
Conditioning regimen					
Chemotherapy	NA	55 (60)		31 (17)	
Chemotherapy and TBI	NA	37 (40)		153 (83)	

SD indicates standard deviation; HCT, hematopoietic cell transplantation; BM, bone marrow; PBSC, peripheral blood stem cells; TBI, total body irradiation; NA, not applicable.

*P-value for comparison between siblings and Hodgkin's lymphoma survivors.

†P-value for comparison between siblings and non-Hodgkin's lymphoma survivors.

follow-up and 115 either actively or passively refused participation (27%). Participants did not differ from nonparticipants by time since transplant, stem cell source, sex, treating institution, or diagnosis. Participants were more likely to have received TBI as part of their conditioning regimen (69.1% versus 59.1%, $P = .04$), and were older at the time of interview (median age 46 [range: 21-73] years versus 42 [range: 18-73] years) than nonparticipants.

Characteristics of the study participants are shown in Table 1. Compared to siblings (median age 44 [range: 19-79] years), HL survivors were younger (median age 40 [range: 22-63] years), whereas NHL survivors were older (median age 51 [range: 23-73] years) at the time of survey administration. There were no race/ethnicity differences between siblings and NHL survivors; however, HL survivors were more likely to be of non-White race/ethnicity compared to siblings (14% versus 7%, $P = .04$). Both HL and NHL survivors were more likely to be males.

When compared to NHL, the demographic and treatment characteristics of HL group were similar, except HL survivors were younger in age both at the time of interview and at HCT, and a higher proportion of NHL survivors received TBI as a part of their conditioning regimen (83% versus 40%, $P < .001$). Overall, 66% of the patients received peripheral blood stem cells (PBSC).

Organ-System and Organ Impairments

Table 2 lists the prevalence of selected medical late effects in HL and NHL HCT survivors. Compared to siblings, lymphoma survivors (HL and NHL combined) were more likely to develop the following organ-system and organ impairments: eye impairments (19.2% versus 11.3%, $P = .01$) including cataracts (14.5% versus 3.8%, $P < .001$); oral health impairments (17.8% versus 12.9%, $P = .05$), including dry mouth (13.8% versus 0.9%, $P < .001$) and problems chewing or swallowing (4.7% versus 1.3%, $P = .009$); endocrine impairments (22.5% versus 11.3%, $P < .001$) including hypothyroidism (18.8% versus 7.2%, $P < .001$); bone impairments (7.2% versus 2.5%, $P = .007$), including osteoporosis (4.3% versus 2.2%, $P = .05$) and avascular necrosis (3.3% versus 0.3%, $P = .04$); neurosensory impairments (32.6% versus 20.4%, $P = .002$), including abnormal sense of taste or smell (12.3% versus 0.6%, $P < .001$) and abnormal sense of touch (20.7% versus 9.7%, $P < .001$); and neuromotor impairments (9.8% versus 6.3%, $P = .06$) including abnormal balance, tremor, or weakness (9.8% versus 5.4%, $P = .02$). Although lymphoma survivors were no more likely than siblings to report overall cardiopulmonary impairments, they did have a higher risk of developing congestive heart failure (4% versus 0.3%, $P = .009$), exercise induced shortness of breath (9.8% versus 2.5%, $P < .001$), and blood clots in the extremities (4.7% versus 1.3%, $P = .03$). There was no

Table 2. *Frequency and Percentage of Selected Self-Reported Late Effects*

	Siblings	Hodgkin Lymphoma Survivors		Non-Hodgkin Lymphoma Survivors		All Lymphoma Survivors	
Late Effects*	N (%)	N (%)	*P*-Value†‡	N (%)	*P*-Value‡§	N (%)	*P*-Value‡#
Number	319 (100)	92 (100)	—	184 (100)	—	276 (100)	—
Eye impairments	36 (11)	11 (12)	.17	42 (23)	.01	53 (19)	.01
Cataracts	12 (4)	8 (9)	.001	32 (18)	<.001	40 (15)	<.001
Glaucoma	6 (2)	0 (0)	.96	0 (0)	.96	0 (0)	.95
Dry eyes	26 (8)	6 (7)	.82	13 (7)	.64	19 (7)	.75
Oral health impairments	41 (13)	11 (12)	.90	38 (21)	.01	49 (18)	.05
Dry mouth	3 (1)	6 (7)	.002	32 (17)	<.001	38 (14)	<.001
Swollen or bleeding gums	35 (11)	3 (3)	.04	6 (3)	.01	9 (3)	.002
Problems chewing or swallowing	4 (1)	5 (5)	.02	8 (4)	.04	13 (5)	.009
Endocrine impairments	36 (11)	28 (30)	<.001	34 (19)	.02	62 (23)	<.001
Hypothyroid	23 (7)	26 (28)	<.001	26 (14)	.0004	52 (19)	<.001
Diabetes	10 (3)	3 (3)	.69	7 (4)	.90	10 (4)	.99
Hyperthyroid	5 (2)	2 (2)	.36	3 (2)	.79	5 (2)	.54
Thyroid nodules	8 (3)	0 (0)	.96	1 (0.5)	.17	1 (0.4)	.09
Bone impairments	8 (3)	4 (4)	.03	16 (9)	.007	20 (7)	.007
Osteoporosis	7 (2)	1 (1)	.36	11 (6)	.04	12 (4)	.05
Avascular necrosis	1 (0.3)	3 (3)	.05	6 (3)	.06	9 (3)	.04
Cardiopulmonary impairments	83 (26)	17 (19)	.50	43 (23)	.06	60 (22)	.08
Arrhythmia	17 (5)	6 (7)	.28	12 (7)	.95	18 (7)	.57
Congestive heart failure	1 (0.3)	4 (4)	.01	7 (4)	.02	11 (4)	.009
Coronary heart disease	13 (4)	2 (2)	.39	8 (4)	.88	10 (4)	.78
Hypertension	61 (19)	6 (7)	.02	10 (5)	<.001	16 (6)	<.001
Stroke	1 (0.3)	0 (0)	.99	0 (0)	.95	0 (0)	.96
Exercise induced dyspnea	8 (3)	7 (8)	.005	20 (11)	.001	27 (10)	<.001
Pericarditis	0 (0)	1 (1)	.95	3 (2)	.95	4 (2)	.93
Stiff or leaking heart valves	7 (2)	3 (3)	.16	2 (1)	.27	5 (2)	.91
Blood clot in extremities	4 (1)	3 (3)	.15	10 (5)	.05	13 (5)	.03
Gastrointestinal impairments	29 (9)	8 (9)	.57	17 (9)	.59	25 (9)	.88
Gall stones	16 (5)	0 (0)	.95	9 (5)	.77	9 (3)	.36
Hepatitis	6 (2)	3 (3)	.37	6 (3)	.57	9 (3)	.37
Esophagus stricture or scarring	11 (3)	5 (5)	.22	3 (2)	.08	8 (3)	.49
Neurosensory impairments	65 (20)	22 (24)	.13	68 (37)	.001	90 (33)	.002
Blind	5 (2)	0 (0)	.96	1 (0.5)	.31	1 (0.4)	.21
Tinnitus or ringing in ears	24 (8)	6 (7)	.67	13 (7)	.47	19 (7)	.74
Complete or partial deafness	8 (3)	2 (2)	.78	10 (5)	.37	12 (4)	.38
Dizziness or vertigo	10 (3)	3 (3)	.36	2 (1)	.11	5 (2)	.37
Abnormal sense of taste or smell	2 (1)	6 (7)	.005	28 (15)	<.001	34 (12)	<.001
Abnormal sense of touch	31 (10)	15 (16)	.02	42 (23)	<.001	57 (21)	<.001
Neuromotor impairments	20 (6)	10 (11)	.02	17 (9)	.29	27 (10)	.06
Paralysis	3 (1)	0 (0)	.95	1 (0.5)	.61	1 (0.4)	.44
Balance, tremor or weakness	17 (5)	10 (11)	.006	17 (9)	.13	27 (10)	.02

*Within an organ system, subjects could have impairment of more than 1 organ.
†*P*-value for comparison between siblings and Hodgkin lymphoma survivors.
‡*P*-values from generalized estimating equations adjusted for age at survey and sex and including variance component for intrafamily correlation. Fisher's exact test used for cell sizes <5.
§*P*-value for comparison between siblings and non-Hodgkin lymphoma survivors.
#*P*-value for comparison between siblings and all lymphoma survivors.

significant difference between HL and NHL survivors in the reported prevalence of any medical late effects.

Functional Limitations

The prevalence of functional impairments following HCT is detailed in Table 3. Lymphoma survivors were more likely than siblings to report that their current health prevented them from attending work or school (15.6% versus 2.2%). Lymphoma survivors were also less likely than siblings to rate their present health as good, very good, or excellent (83.7% versus 94.7%). There was no significant difference between HL and NHL survivors in the reported frequencies of various functional limitations and overall health.

Predictors of Late Effects

Table 4 shows multivariate models with the relative odds of developing selected late effects and functional limitations based on lymphoma type (HL versus NHL), use of TBI as a part of the conditioning reg-

Table 3. *Frequency and Percentage of Self-Reported Health Status and Functional Impairments*

Health Status and Functional Impairment	Siblings	Hodgkin Lymphoma Survivors		Non-Hodgkin Lymphoma Survivors		All Lymphoma Survivors	
	N (%)	N (%)	*P*-Value*†	N (%)	*P*-Value*‡	N (%)	*P*-Value*§
Number	319 (100)	92 (100)		184 (100)		276 (100)	
Need assistance with activities of daily living			.59		.04		.18
Yes	1 (0.3)	0 (0.0)		4 (2.2)		4 (1.4)	
No	318 (99.7)	92 (100.0)		180 (97.8)		272 (98.6)	
Need assistance with routine activities			.36		.05		.06
Yes	8 (2.5)	4 (4.3)		11 (6.0)		15 (5.4)	
No	311 (97.5)	88 (95.7)		173 (94.0)		261 (94.6)	
Health prevents work or school attendance			<.001		<.001		<.001
Yes	7 (2.2)	15 (16.3)		28 (15.2)		43 (15.6)	
No	312 (97.8)	77 (83.7)		156 (84.8)		233 (84.4)	
General health			<.001		<.001		<.001
Poor/fair	17 (5.3)	16 (17.4)		29 (15.8)		45 (16.3)	
Good	66 (20.7)	32 (34.8)		56 (30.4)		88 (31.9)	
Very good	156 (48.9)	31 (33.7)		65 (35.3)		96 (34.8)	
Excellent	80 (25.1)	13 (14.1)		34 (18.5)		47 (17.0)	

**P*-values from generalized estimating equations adjusted for age and sex and including variance component for intrafamily correlation. Fisher's exact test used for cell sizes <5.

†*P*-value for comparison between siblings and Hodgkin lymphoma survivors.

‡*P*-value for comparison between siblings and non-Hodgkin lymphoma survivors.

§*P*-value for comparison between siblings and all lymphoma survivors.

imen, and sex. After adjusting for age at transplantation and age at survey, females had a higher risk of developing osteoporosis (odds ratio [OR] 8.7, 95% confidence interval [CI] 1.8-41.7), congestive heart failure (OR 4.3, 95% CI 1.1-17.2), and balance impairment, tremor, or weakness (OR 2.4, 95% CI 1.0-5.5) compared to males. The relative odds of developing cataracts and dry mouth were 4.9 times (95% CI 1.5-15.5) and 3.4 times (95% CI 1.1-10.4) higher, respectively, in survivors who had received TBI as a part of their conditioning regimen compared to those who did not. The type of lymphoma had no impact on the risk of developing any organ specific late effects or functional limitations.

DISCUSSION

The current study demonstrates that HL and NHL survivors treated with autologous HCT have a higher prevalence of a wide spectrum of medical late complications and functional limitations, and are more likely to have a negative perception of their overall health status compared to their siblings. Furthermore, medical late effects can lead to considerable functional impairments as evidenced by a significantly large proportion of survivors being unable to attend work or school because of health problems and grading their overall health status as only poor to fair.

Nonneoplastic late effects of autologous HCT in lymphoma survivors have not been well characterized previously. Ruiz-Soto et al. [12] studied late toxicity, defined as adverse events occurring 30 days after transplantation, in 158 recipients of autologous HCT for aggressive NHL. Forty-three patients developed late toxicity; common late adverse events included infections (19%), neurologic (18%), digestive tract (15%), endocrine (9%), and pulmonary (9%) problems. However, inclusion of patients in their early posttransplant period, a short duration of posttransplant follow-up (median followup was 3 years, range: 0.2-10 years), and a lack of a control group were limitations of their study. Lavoie et al. [13] have reported long-term outcomes of 53 HL survivors followed for at least 10 years or more following autologous HCT. In this retrospective analysis, common nonmalignant late complications included hypothyroidism (38%), hypogonadism (38%), infections (34%), anxiety or depression (13%), and cardiac diseases (9%).

Survivors of HL and NHL treated with chemotherapy and/or radiation therapy are at an increased risk for developing late onset cardiovascular and pulmonary complications, primarily from toxicity associated with the use of anthracyclines, bleomycin, and mediastinal irradiation [14-22]. Lymphoma survivors in our study reported a higher prevalence of congestive heart failure, exercise-induced shortness of breath, and blood clots in the extremities. However, the risk of myocardial infarction, coronary artery disease, angina, valvular heart disease, stroke, and lung

Table 4. *Relative Odds of Having Selected Late Effects Based on Type of Lymphoma, Use of Total-Body Irradiation (TBI) in Conditioning Regimen, and Sex*

	Odds Ratio	95% CI	*P*-Value
Cataracts			
Hodgkin lymphoma	1.1	0.4-3.0	.79
TBI	4.9	1.5-15.5	.007
Female	1.1	0.6-2.3	.72
Dry mouth			
Hodgkin lymphoma	0.5	0.2-1.4	.17
TBI	3.4	1.1-10.4	.03
Female	1.5	0.7-3.1	.26
Osteoporosis			
Hodgkin lymphoma	0.3	0.03-2.9	.31
TBI	1.6	0.3-8.4	.57
Female	8.7	1.8-41.7	.007
Congestive heart failure			
Hodgkin lymphoma	2.4	0.5-11.8	.27
TBI	0.8	0.2-3.2	.77
Female	4.3	1.1-17.2	.04
Balance impairment, tremor, or weakness			
Hodgkin lymphoma	1.1	0.4-3.1	.83
TBI	0.6	0.3-1.6	.32
Female	2.4	1.0-5.5	.04

For each variable, odds ratios were adjusted for the other variables with further adjustment for age at transplantation and age at survey.

CI indicates confidence interval.

fibrosis was comparable to that of siblings. This low prevalence of specific cardiopulmonary outcomes could result from the relatively young age of our study participants, both subjects and siblings, and the relatively short duration of follow-up after transplantation.

Female lymphoma survivors were at an increased risk of developing congestive heart failure and osteoporosis. In a previous study, we have observed female autologous HCT recipients to have a 4-fold higher risk of late death from cardiac complications compared to age- and sex-matched general population controls [1]. Although previous studies have not demonstrated a sex preference in the risk of osteoporosis after autologous HCT [23,24], ovarian ablation secondary to high-dose chemotherapy and TBI could possibly explain the increased risk of this late effect in females. Nonetheless, modifiable risk factors for cardiac disease and osteoporosis should be identified early and appropriately managed in lymphoma survivors of autologous HCT, especially females.

Compared to siblings, survivors in our study had a greater likelihood of having functional impairments and an adverse perception of their overall health status. Although no other study has specifically characterized functional limitations in lymphoma survivors, similar observations have been described previously in studies that have included recipients of autologous HCT for hematologic disorders [25-27]. In a self-reported survey administered serially over the first 2 years posttransplant by Lee et al. [26], a large proportion of autologous HCT survivors were observed to have persistent functional restrictions over time.

Thirty-five percent of the eligible cohort did not participate in this study, and the participants were older at study participation than the nonparticipants; this could be a potential source of bias for our study. However, comparison with the siblings was age adjusted. Furthermore, the results of this study are based on self-reported medical information and could possibly result in misclassification of the outcomes of interest. To overcome this limitation, a validation study was conducted on HCT recipients at City of Hope National Medical Center, and demonstrated that self-report of complications using the BMT-SS questionnaire has good to excellent agreement with data abstracted from medical records [10]. Additionally, the sibling comparison group also self-reported data, hence eliminating any systematic differences in bias between the 2 comparison groups. There is also a potential for overdetection bias in our study, with more vigilance for specific late effects in HCT survivors compared to healthy sibling controls. Finally, we did not account for other known risk factors for several outcomes, such as family history, smoking history, activity level, and pretransplant therapy, in our analyses. These pretransplant exposures, especially prior chemotherapy and radiation therapy, can independently increase the risk of developing specific late complications in lymphoma survivors. However, the risk of these late complications may be further compounded by the high-dose chemotherapy and TBI routinely used as a part of the conditioning regimen for autologous HCT.

These limitations notwithstanding, our study comprehensively describes the magnitude of risk of medical late effects and functional limitations, and evaluates risk factors for these outcomes in HL and NHL survivors of autologous HCT. This study demonstrates that long-term survivors are at increased risk of late effects that results in functional limitations and therefore provides the justification for continued monitoring and surveillance of this population using published guidelines [28].

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