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Scientific Article

Long-Term Toxicity after Non-Myeloablative Conditioning Regimens Using Total Body Irradiation

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Purpose: To evaluate long-term health risks after allogeneic hematopoietic stem cell transplantation (HSCT) using non-myeloablative total body irradiation (TBI).

Methods and Materials: All adult patients undergoing non-myeloablative allogeneic HSCT using TBI-based conditioning from 1995 to 2020 at our institution were included. Long-term toxicities, defined as events persisting beyond or occurring after 6 months from the date of transplant, were graded per the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0. A competing risk analysis was performed to assess the risk of developing long-term toxicities within major organ systems using the Fine-Gray model. Outcomes were compared with a cohort of patients undergoing myeloablative TBI.

Results: A total of 174 patients undergoing nonmyeloablative HSCT were assessed along with 378 myeloablative patients. Nonmyeloablative recipients were older (58 vs 43 years, $P < .001$), less likely to be transplanted for acute leukemia (35% vs 64%, $P < .001$), more likely to be transplanted for non-malignant conditions (33% vs 11%, $P < .001$), and were more likely to have used tobacco (33% vs 22%, $P = .009$). The median follow-up was 7.4 years. The cumulative incidences of long-term toxicities at 5 years for nonmyeloablative and myeloablative patients, taking into account the competing risk of death, were pulmonary (4% vs 4.8%, $P > .9$), cardiac (6.8% vs 3.3%, $P = .11$), renal (4.3% vs 4.1%, $P = .9$), thyroid (3.6% vs 1.5%, $P = .2$), other endocrine (3.1% vs 8.8%, $P = .04$), and cataracts (2.5% vs 2.8%, $P = .7$). The risk of developing a secondary malignancy was 3.5% vs 1.1% ($P = .2$) between the 2 cohorts. The proportion of all toxicities that were high-grade (3-5) for nonmyeloablative and myeloablative regimens, respectively, were pulmonary (60% and 69%), cardiac (17% and 45%), renal (27% and 21%), and other endocrine (4% and 2%).

Conclusions: Recipients of nonmyeloablative conditioning regimens, despite receiving much lower doses of TBI and chemotherapy, are at risk of developing significant, long-term medical conditions comparable with those undergoing myeloablative HSCT.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is often used for patients with high-risk hematologic malignancies and select nonmalignant conditions.

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Although the conditioning regimen contributes, the graft-versus-tumor effect is the primary mechanism whereby tumor cells are eradicated. Allogeneic HSCT is preceded by a conditioning regimen that prepares the patient to accept the donor stem cells. The majority of conditioning regimens consist of cytotoxic chemotherapy, with or without total body irradiation (TBI). Conditioning regimens are broadly grouped into those that are myeloablative and those that are nonmyeloablative. Myeloablative conditioning provides maximal cytoreduction before transplant in addition to the graft-versus-tumor effect. While myeloablative conditioning is associated with a higher risk of nonrelapse mortality, younger patients with acute leukemia or myelodysplastic syndromes benefit from this approach.[1] Nonmyeloablative conditioning is better tolerated and allows HSCT to be performed in older or more frail patients.

While allogeneic HSCT has the potential to cure patients of diseases that would otherwise prove fatal, it is associated with significant complications and a relatively high risk of treatment-related mortality. Transplant patients are complex, and it is often difficult to attribute toxicities to a specific component of the treatment program. Several studies have evaluated long-term risks after TBI-based myeloablative allogeneic HSCT.[2-8] However, the risk of late complications after nonmyeloablative HSCT (in which patients often receive a single 2 Gy dose of TBI and lower doses of chemotherapy) has not been comprehensively studied.[8,9]

Because outcomes after allogeneic HSCT improve with better survivorship care and risk-adapted treatment,[10] understanding the long-term toxicities after transplant is becoming increasingly relevant. Importantly, there have been far fewer studies evaluating nonmyeloablative regimens, despite their increasing use. In this study, we reviewed all patients at our institution who underwent an allogeneic HSCT, with both nonmyeloablative and myeloablative TBI-based conditioning, to report the risk of late complications between these 2 populations.

Methods and Materials

This institutional review board-approved study evaluated all adult (aged ≥18 years old) patients undergoing allogeneic HSCT at Duke University Medical Center. Those treated with a TBI-based conditioning regimen between January 1, 1995, and December 31, 2020, were included in the analysis. Comprehensive patient, disease, and treatment-related characteristics were extracted from each patient's medical record, with particular attention to complications and sequelae after transplant.

TBI was delivered using a uniform technique throughout the study period and has been previously described in detail.[11] Briefly, myeloablative TBI typically consisted of 12 to 13.5 Gy in 1.5 Gy twice-a-day fractions with the lung dose attenuated to 8 to 10 Gy. Nonmyeloablative TBI was typically 2 Gy in a single fraction. A testicular boost consisting of 4 Gy in 2 fractions has consistently been administered to all patients undergoing HSCT for acute lymphoid leukemia (ALL). During the early study period, a testicular boost was also given to patients with acute myeloid leukemia (AML). A craniospinal boost before TBI was administered to patients undergoing transplant for ALL who had a history of central nervous system disease involvement.

In conjunction with TBI, all patients also received chemotherapy as part of their conditioning regimen depending on the underlying disease and other factors. Patients receiving myeloablative TBI-based conditioning most commonly received one of the following drug regimens: cyclophosphamide (n = 118; 31%), fludarabine (n = 73; 19%), fludarabine and thiotepa (n = 57; 15%), etoposide (n = 31; 8%), and cyclophosphamide and fludarabine (n = 21; 6%). The most commonly prescribed agents in nonmyeloablative TBI-based regimens were fludarabine and cyclophosphamide (n = 35; 20%), fludarabine, cyclophosphamide, and alemtuzumab (n = 17; 10%), and fludarabine, cyclophosphamide, and antithymocyte globulin (n = 12; 7%). Graft sources included matched siblings, unrelated donors, haploidentical donors, and umbilical cord blood.

Long-term toxicities were defined as new medical conditions developing after HSCT that persisted beyond or developed after 6 months from the date of transplant. For this study, we collected data on pulmonary, cardiac, renal, and endocrine toxicities, in addition to the development of cataracts and secondary malignancies. Toxicities were graded per the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

All eligible patients undergoing transplant were included. Baseline characteristics were compared between the myeloablative and nonmyeloablative patient groups using the *t* test or Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. Median follow-up was calculated using the reverse Kaplan-Meier method. A competing risk analysis was performed to assess the risk of developing long-term toxicities within major organ systems using the Fine-Gray model, taking into account death as a competing event. Events included new medical conditions developing after HSCT that persisted beyond or developed after 6 months from the date of transplant. Medical conditions that developed before 6 months of HSCT and resolved were not scored. Gray's test was used to test for significant differences in risk between transplant types. The Kaplan-Meier method was used to estimate overall survival. The

log-rank test was used to test for significant differences in overall survival between transplant groups.

Associations between predictor variables and toxicity outcomes were investigated using logistic regression. Factors included in an initial univariate analysis (UVA) were age at transplant, sex, history of tobacco use, pretransplant pulmonary and/or cardiac disease, pulmonary function, prior radiation therapy, diagnosis, stage of disease at transplant, donor source, and intensity of transplant (myeloablative vs nonmyeloablative). For patients undergoing myeloablative conditioning, the degree of lung attenuation and heterogeneity corrections was also included when assessing the risk of pulmonary complications. Factors significant to UVA were included in a final multivariate (MVA) model as appropriate. All statistical analyses were conducted using SAS 9.4 and R Studio (Version 4.2.2).

Results

A total of 552 adult patients undergoing allogenic HSCT during the specified time frame were assessed. This included 174 nonmyeloablative and 378 myeloablative TBI-based conditioning recipients. Median follow-up was 7.4 years (myeloablative, 7.9 years; nonmyeloablative, 5.8 years). As expected, significant differences were noted between these 2 cohorts. Recipients of nonmyeloablative regimens were older (58 vs 43 years, $P < .001$), less likely to be transplanted for acute leukemia (35% vs 64%, $P < .001$), more likely to be transplanted for nonmalignant conditions (33% vs 11%, $P < .001$), and were more likely to have used tobacco (33% vs 22%, $P = .009$). Comprehensive patient characteristics are found in Table 1.

Pulmonary

Pretransplant pulmonary disease was evenly distributed between nonmyeloablative (6%) and myeloablative (7%) patients ($P = .67$). Similarly, baseline pulmonary function tests were not different (forced expiratory volume in 1 second, 85% vs 87%, $P = .18$; diffusing capacity of the lungs for carbon monoxide, 76% vs 79%, $P = .79$).

The 5- and 10-year cumulative risk of developing pulmonary complications, taking into account the competing risk of death, was 4% versus 4.8% and 7.3% versus 11% for nonmyeloablative and myeloablative HSCT, respectively ($P > .9$) (Fig. 1). The proportion of all pulmonary toxicities that were grades 3 to 5 for these 2 cohorts was 60% and 69%, respectively. For all patients, the most common toxicities included infectious pneumonia (40%), respiratory failure, not otherwise specified (18%), and dyspnea, not otherwise specified (10%) (Table 2). Only 3 patients had documented pneumonitis 6 months or longer after transplant (1 grade 2 case after nonmyeloablative HSCT; 2 grade 3 cases after myeloablative HSCT). On UVA, no factors were significantly associated with a higher risk of pulmonary complications. For the subset of patients undergoing myeloablative conditioning, the degree of lung attenuation and utilization of heterogeneity corrections (not applicable for nonmyeloablative HSCT) were not associated with pulmonary complications.

Cardiac

Pretransplant cardiac disease was more common in nonmyeloablative patients (22% vs 15%, $P = .038$). The most common cardiac comorbidities were hypertension (57%), arrhythmias (18%), and ischemic heart disease (10%). Of those with available data, 86% had a normal ejection fraction (> 55%) before transplant.

The 5- and 10-year risk of developing cardiac complications was 6.8% versus 3.3% and 11% versus 5.6% for nonmyeloablative and myeloablative HSCT, respectively ($P = .11$) (Fig. 2). The proportion of all toxicities that were high-grade for these 2 cohorts was 17% and 45%, respectively. For all patients, the most common toxicities included heart failure (21%), myocardial infarction (14%), and left ventricular systolic dysfunction (12%) (Table 2). The only variable significant for an increased risk of cardiac complications on UVA was the increasing number of pretransplant chemotherapy regimens (hazard ratio [HR], 2.34; 95% CI, 1.03-5.31; $P = .04$).

Renal

Median baseline creatinine level was 0.8 mg/dL (interquartile range, 0.7-1). The 5- and 10-year risk of developing renal complications was 4.3% versus 4.1% and 9.3% versus 6.4% for nonmyeloablative and myeloablative HSCT, respectively ($P = .9$) (Fig. 3). The proportion of all toxicities that were high-grade for these 2 cohorts was 27% and 21%, respectively. For all patients, the most common toxicities included chronic kidney disease (70%) and elevated creatinine levels, the latter of which applied to creatinine level elevations of unspecified etiology, including acute kidney injury (23%). On UVA, male sex (HR, 3.50; 95% CI, 1.56-7.86; $P = .002$) and higher posttransplant baseline creatinine levels (HR, 1.13; 95% CI, 1.03-1.24; $P = .01$) were associated with a higher risk of complications. On MVA, only the male sex remained significant (HR, 3.44; 95% CI, 1.52-7.77; $P = .003$).

Thyroid

The 5- and 10-year risk of developing thyroid complications was 3.6% versus 1.5% and 3.6% versus 2.8% for nonmyeloablative and myeloablative HSCT, respectively

Table 1 Baseline characteristics by transplant type

Characteristic	Myeloablative (n = 378)	Nonmyeloablative (n = 174)	Overall (n = 552)	*P*-value
Age (y)				< .001
Median [range]	43 [19-68]	58 [21-80]	46 [19-80]	
Sex				.899
Female	144 (38%)	68 (39%)	212 (38%)	
Male	234 (62%)	106 (61%)	340 (62%)	
Race				.189
White	282 (75%)	142 (82%)	424 (77%)	
Black or African American	70 (19%)	24 (14%)	94 (17%)	
Asian	10 (3%)	2 (1%)	12 (2%)	
Other or unknown	16 (3%)	6 (3%)	22 (4%)	
Smoking history				.009
Yes	85 (22%)	58 (33%)	143 (26%)	
No	293 (78%)	116 (67%)	409 (74%)	
Pack-years smoked*				.002
Median [range]	10 [0.5-60]	20 [0.5-120]	14 [0.5-120]	
Pretransplant pulmonary disease				.67
Yes	27 (7%)	10 (6%)	37 (7%)	
No	351 (93%)	164 (94%)	515 (93%)	
FEV1				.179
Median [range]	87 [31-128]	85 [38-126]	87 [11-128]	
DLCO (corrected for anemia)				.788
Median [range]	79 [38-138]	76 [36-121]	78 [36-138]	
Pretransplant cardiac disease				.038
Yes	56 (15%)	39 (22%)	95 (17%)	
No	322 (85%)	135 (78%)	457 (83%)	
Prior radiation therapy				.264
Yes	48 (12.7%)	29 (16.7%)	77 (13.9%)	
No	330 (87.3%)	145 (83.3%)	475 (86.1%)	
Diagnosis				< .001
AML/ALL	242 (64%)	61 (35%)	303 (55%)	
NHL/HL	68 (18%)	28 (16%)	96 (17%)	
MDS	26 (7%)	27 (16%)	53 (10%)	
Other	42 (11%)	58 (33%)	100 (18%)	
Prior chemotherapy regimens Median [range]	2 [0-7]	2 [0-7]	2 [0-7]	.004
State of disease at transplant				< .001
CR1	167 (44%)	50 (29%)	217 (39%)	
CR2/CR3	136 (36%)	35 (20%)	171 (31%)	
Partial response/relapse	38 (10%)	25 (14%)	63 (12%)	
N/A	37 (10%)	64 (37%)	101 (18%)	

(*continued on next page*)

Table 1 (*Continued*)

Characteristic	Myeloablative (n = 378)	Nonmyeloablative (n = 174)	Overall (n = 552)	*P*-value
Donor source				< .001
Matched sibling	104 (27%)	44 (25%)	148 (27%)	
Matched URD	105 (28%)	36 (21%)	141 (25%)	
Haploidentical	7 (2%)	42 (24%)	49 (9%)	
Umbilical cord blood	161 (43%)	38 (22%)	199 (36%)	
Other	1 (< 1%)	14 (8%)	15 (3%)	

Abbreviations: ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; CR = complete remission; DLCO = diffusing capacity of the lungs for carbon monoxide; FEV1 = forced expiratory volume in 1 second; HL = Hodgkin lymphoma; MDS = myelodysplastic syndrome; N/A = not applicable; NHL = non-Hodgkin lymphoma; URD = unrelated donor.
*of current/former smokers

(*P* = .2) (Fig. 4). There were no grades 3 to 5 thyroid complications. The most common toxicity was grades 1 to 2 primary hypothyroidism (95%) (Table 2). On UVA, increasing age at transplant (HR, 1.03; 95% CI, 1-1.07; *P* = .05) and nonmyeloablative conditioning (HR, 2.43; 95% CI, 1.02-5.77; *P* = .04) were associated with an increased risk of thyroid complications. However, neither variable was associated with a higher risk of MVA.

Other Endocrine

The 5- and 10-year risk of developing other endocrine complications was 3.1% versus 8.8% and 10% versus 16% for nonmyeloablative and myeloablative HSCT, respectively (*P* = .04) (Fig. 5). The proportion of all toxicities that were high-grade for these 2 cohorts was 2% and 4%, respectively. For all patients, the most common toxicities included adrenal insufficiency (21%), testosterone deficiency (23%), and hyperglycemia (17%) (Table 2). No significant associations with a higher risk of complications were found on UVA.

Cataracts

The 5- and 10-year risk of developing cataracts was 2.5% versus 2.8% and 8% versus 8.6% for

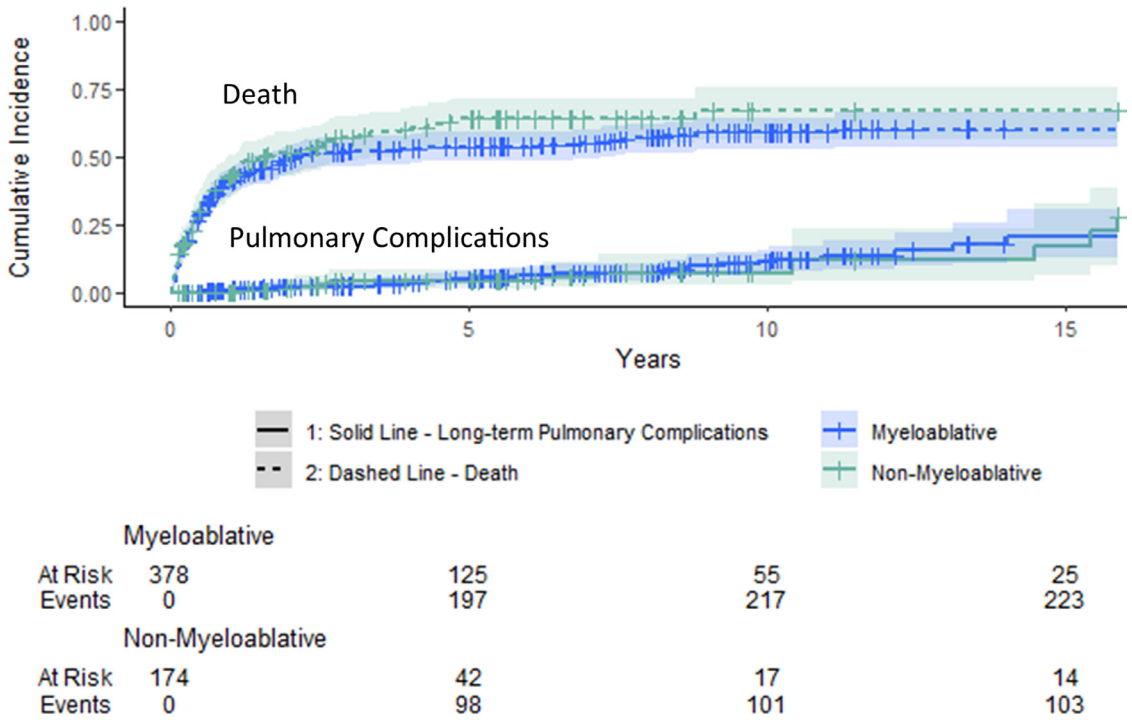

Figure 1 Cumulative incidence of long-term pulmonary complications by transplant type (with competing risk of death).

Table 2 Toxicities by organ system*

Organ system	Myeloablative (n = 378)	Nonmyeloablative (n = 174)	All (n = 552)
Pulmonary (grades, 1-2)			
Pneumonia	7	2	9
Thromboembolic event	3	2	5
Dyspnea, NOS	2	2	4
Other	10	2	12
Pulmonary (grades, 3-5)			
Pneumonia	20	7	27
Respiratory failure	12	4	16
Dyspnea, NOS	5	0	5
Other	12	1	13
Total	71	20	91
Cardiac (grades, 1-2)			
Atrial fibrillation	2	2	4
Heart failure	0	2	2
Hypertension	2	0	2
Other	6	2	8
Cardiac (grades, 3-5)			
Heart failure	4	3	7
Myocardial infarction	5	1	6
Left ventricular systolic dysfunction	4	1	5
Other	6	2	8
Total	29	13	42
Endocrine (grades, 1-2)			
Hypothyroidism	12	10	22
Hyperthyroidism	1	0	1
Testosterone deficiency	24	2	26
Adrenal insufficiency	18	3	21
Hyperglycemia. NOS	14	4	18
Other	17	3	20
Endocrine (grades, 3-5)			
Adrenal insufficiency	1	2	3
Hyperglycemia	0	1	1
Other	1	0	1
Total	88	25	113

Abbreviation: NOS = not otherwise specified.
*Some patients developed more than 1 toxicity.

nonmyeloablative and myeloablative HSCT, respectively ($P = .4$) (Fig. 6). The overwhelming majority of cases were bilateral (81%). On UVA, only increasing age at transplant was associated with a higher risk (HR, 1.03; 95% CI, 1.00-1.07; $P = .02$).

Secondary malignancies

Overall, 35 patients developed a second malignancy after HSCT. The 5- and 10-year risk of developing a second malignancy was 3.5% versus 1.1% and 6.3% versus

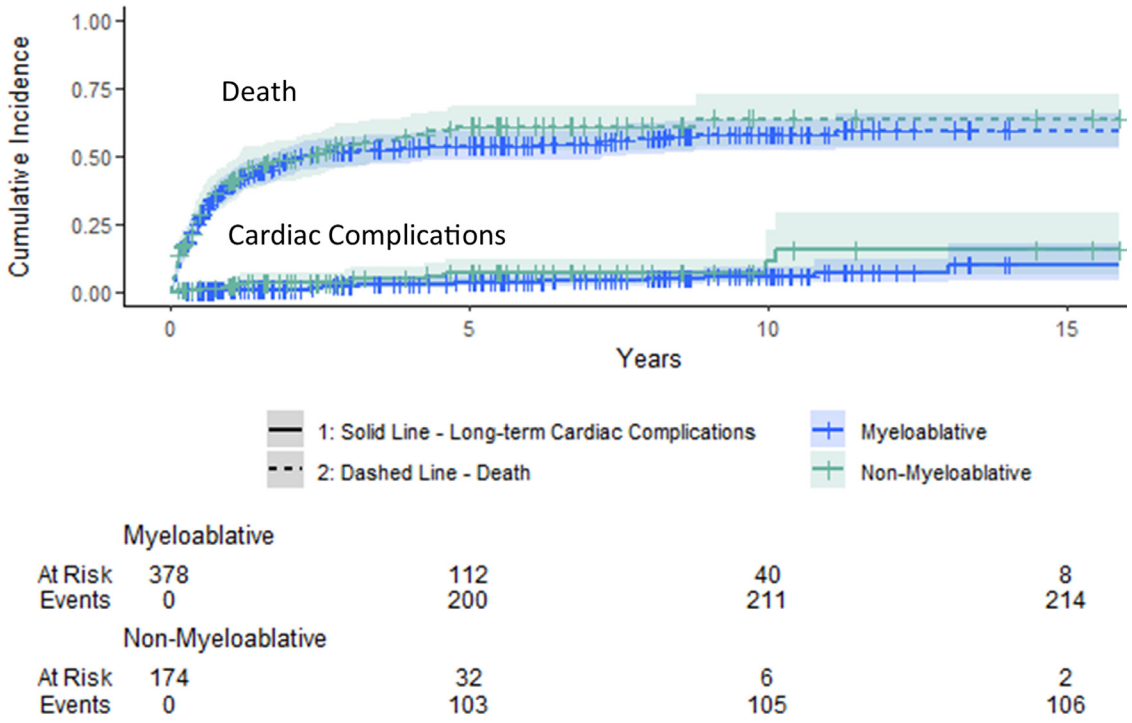

Figure 2 Cumulative incidence of long-term cardiac complications by transplant type (with competing risk of death).

Figure 3 Cumulative incidence of long-term renal complications by transplant type (with competing risk of death).

5.6% for nonmyeloablative and myeloablative HSCT, respectively (P = .2) (Fig. 7). The most common second malignancies were nonmelanoma cutaneous malignancies (n = 18), AML (n = 5), and posttransplant lymphoproliferative disorder (n = 3). None of the patients who developed a secondary AML were transplanted because of myelodysplastic syndrome. On UVA, males were at higher risk of developing a secondary malignancy (HR, 2.76; 95% CI, 1.14-6.72; P = .03), as were patients who underwent nonmyeloablative conditioning (HR, 2.06; 95% CI, 1.01-4.2; P = .05). On MVA, only male sex remained significant (HR, 2.66; 95% CI, 1.09-6.48; P = .03).

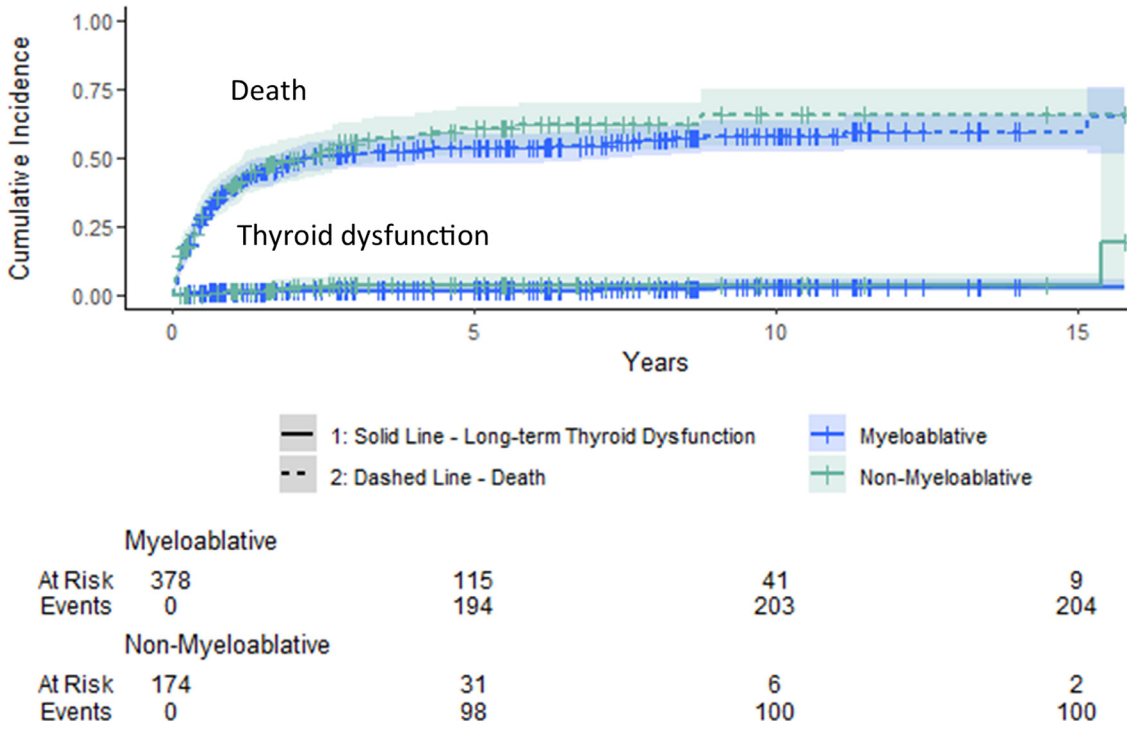

Figure 4 Cumulative incidence of long-term thyroid dysfunction by transplant type (with competing risk of death).

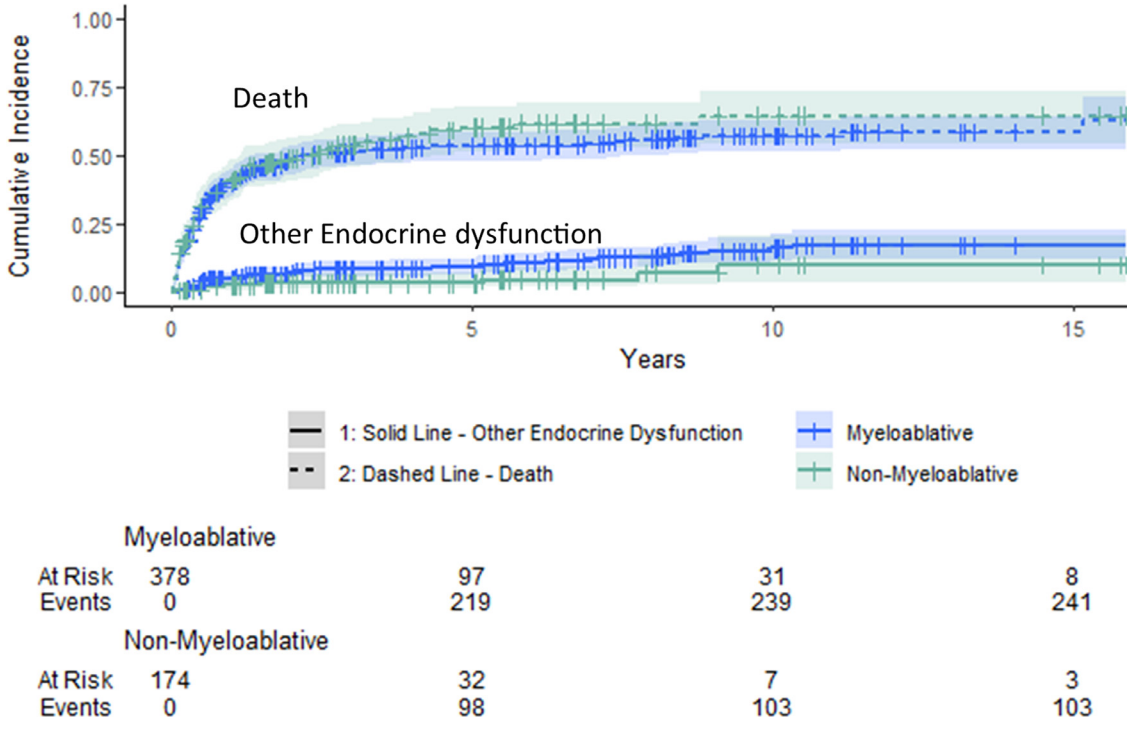

Figure 5 Cumulative incidence of long-term other endocrine dysfunction by transplant type (with competing risk of death).

Overall outcomes

For nonmyeloablative and myeloablative cohorts, respectively, median overall survival was 1.9 years (95% CI, 1.2-3.2; P = .2) and 1.8 years (95% CI, 1.3-3.3; P = .2). Five-year overall survival for all patients was 40% (33% nonmyeloablative; 42% myeloablative).

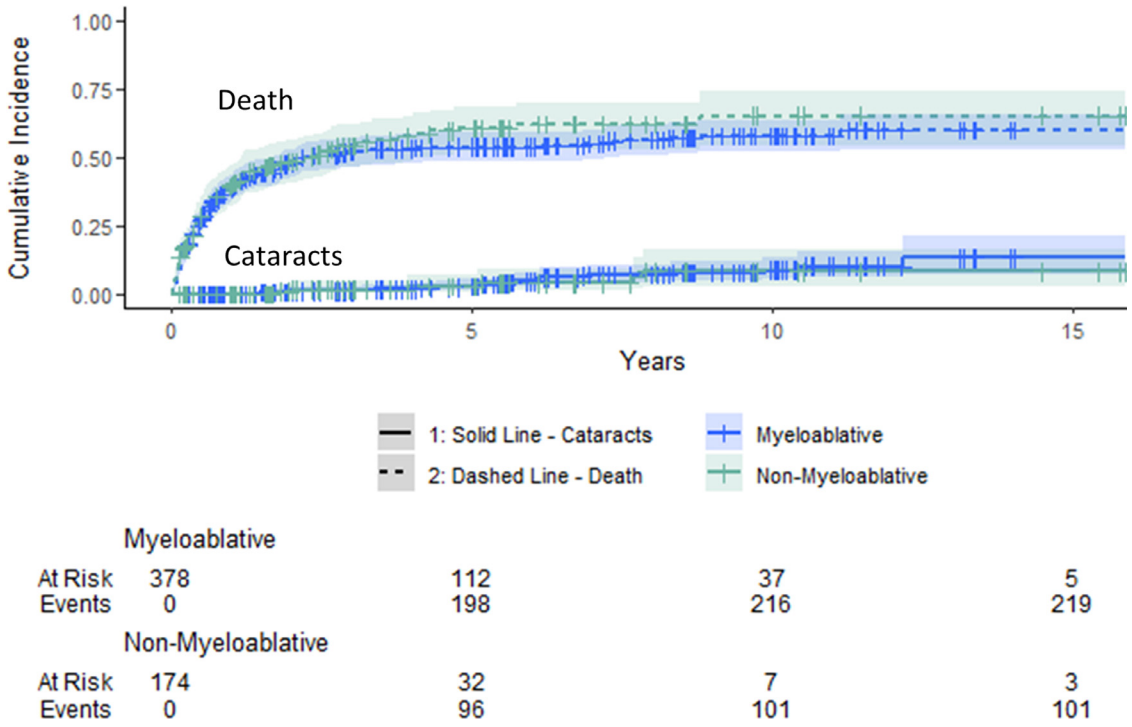

Figure 6 Cumulative incidence of developing cataracts by transplant type (with competing risk of death).

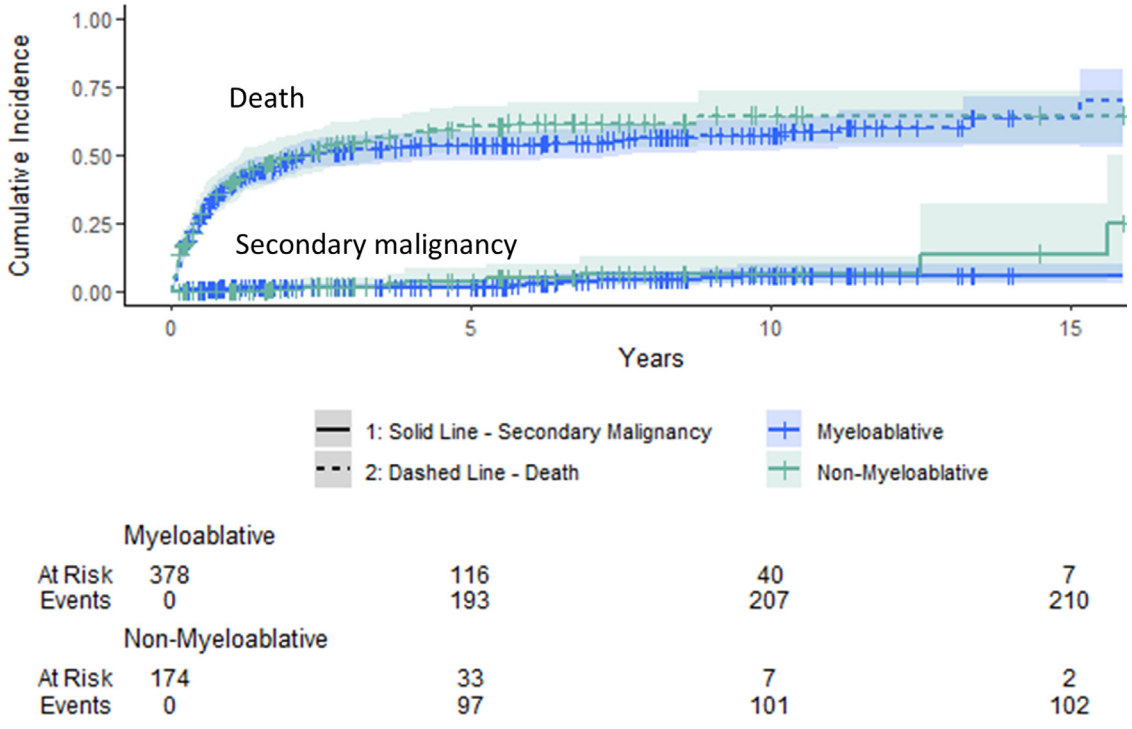

Figure 7 Cumulative incidence of developing a secondary malignancy by transplant type (with competing risk of death).

Discussion

To our knowledge, this is one of the largest studies reporting long-term toxicities in HSCT patients undergoing nonmyeloablative TBI-based conditioning regimens. Our comprehensive analysis demonstrates that the risk of developing long-term medical conditions involving major organ systems is significant, even though

a nonmyeloablative HSCT consists of far lower doses of TBI and chemotherapy compared with a myeloablative HSCT. Understanding the spectrum of potential complications after different treatment approaches provides valuable information for those obtaining informed consent from patients and for survivorship programs. Further, an understanding of long-term risks can inform and guide evolving treatment techniques that are being explored in the setting of HSCT, including volumetric modulated arc-based TBI and total marrow ± lymphoid irradiation.[12-16] The former technique, in particular, provides the coverage of conventional TBI with an improved capability of reducing doses to select organs at risk.

Long-term complications after myeloablative HSCT have been previously reported by numerous investigators.[2-8] Several studies have reported differences in acute toxicities[9,17] between conditioning regimen intensity. One of the few studies that have specifically evaluated long-term risks after nonmyeloablative and myeloablative regimens were from Pearlman et al[8]. The incidence of acute and late adverse effects after both myeloablative (n = 207; 76% allogeneic and 24% autologous) and nonmyeloablative (n = 422, all allogeneic) TBI-based conditioning regimens were evaluated. The study focused primarily on acute toxicity, but select late effects (defined as toxicities developing >90 days after HSCT) were reported. The crude risk of cataracts was 16%. Cataracts developed earlier in the nonmyeloablative cohort. After correcting for age, the risk of cataracts did not differ between cohorts. Only 2 secondary malignancies were diagnosed during the follow-up period. The risks of long-term pulmonary, cardiac, endocrine, and renal complications were not reported.

Given very limited data on long-term risks after nonmyeloablative HSCT, without a comprehensive analysis comparing late toxicities between nonmyeloablative and myeloablative conditioning regimens, we sought to examine our institutional experience. In this analysis, we report specific toxicities in multiple organ systems, graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0, using actuarial statistics adjusted for the competing risk of death to optimally inform providers of the risks of these procedures.

A few findings in the nonmyeloablative cohort were notable. Hypothyroidism and cataracts, 2 toxicities typically ascribed to radiation therapy, developed in ∼ 4% and ∼ 8% of patients, respectively, even in the setting of a single 2 Gy dose of TBI. Long-term renal impairment was also common after nonmyeloablative HSCT (9%) despite almost all patients having normal pretransplant kidney function. The risk of second malignancies was 6% at 10 years. Nonmelanoma skin cancers predominated. Finally, a variety of pulmonary and cardiac conditions developed after nonmyeloablative HSCT, many of which were high-grade.

It is acknowledged that it is difficult to ascribe specific toxicities to discrete components of the transplant (eg, TBI, chemotherapy, and others) or unrelated issues such as advancing age, tobacco use, or other baseline comorbidities. Further, given the heterogeneity of the patient population, it is challenging to directly compare toxicities between the 2 cohorts of patients. Recognizing this difficulty, we simply sought to document significant medical conditions that develop after HSCT and demonstrated that the burden of such is quite similar between those undergoing a much more intense myeloablative transplant and those undergoing a far less intense nonmyeloablative transplant.

Because with all retrospective analyses, this study has notable limitations. Patients undergoing allogeneic HSCT are at high risk of nonrelapse mortality, which reduces the number of patients available for long-term follow-up. This is poignantly illustrated in the cumulative incidence curves for each toxicity. Further, patients undergoing allogeneic HSCT are complex with lengthy medical records. Identifying, categorizing, and grading all toxicities can be challenging. Thus, even though a comprehensive review of all patients was undertaken, some toxicities may have been underreported within the accessible medical record. There are also inherent differences between populations of patients undergoing myeloablative and nonmyeloablative transplants, both regarding underlying diagnoses and the burden of comorbidities. It was not assumed that one group should have a higher or lower risk of long-term toxicity. We simply sought to report cumulative risks in each population.

A UVA and MVA, as appropriate, were performed to evaluate whether certain variables were associated with an increased risk of long-term toxicity. While we included key variables in our UVA that were widely available in the medical record, we likely neglected other important variables that may independently contribute to specific toxicities. Other factors, such as cumulative doses of specific cytotoxic systemic agents, variable prophylaxis patterns, and posttransplant graft-versus-host disease immunosuppression, may confer different risks as well and are difficult to group and control.

Despite these limitations, our report is unique in that it describes the cumulative risk of long-term toxicities developing after both nonmyeloablative and myeloablative TBI regimens and illustrates significant long-term risks with both.

Conclusion

Our unique series demonstrates that recipients of nonmyeloablative TBI-based conditioning regimens are at significant risk of developing long-term medical conditions, similar to those undergoing a myeloablative

HSCT, despite much lower doses of radiation and chemotherapy.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Donna Niedzwiecki was responsible for statistical analysis.

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