REGULAR ARTICLE

blood advances

Late effects after ablative allogeneic stem cell transplantation for adolescent and young adult acute myeloid leukemia

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Key Points

- Nearly 25% of AYAs with AML who were disease-free survivors at 1 year after myeloablative HCT had ≥1 late effects.
- With the exception of cataracts, high-dose TBI exposure was not an independent predictor for malignant or nonmalignant late effects.

There is marked paucity of data regarding late effects in adolescents and young adults (AYAs) who undergo myeloablative conditioning (MAC) allogeneic hematopoietic cell transplantation (HCT) for acute myeloid leukemia (AML). We evaluated late effects and survival in 826 1-year disease-free survivors of MAC HCT for AYA AML, with an additional focus on comparing late effects based upon MAC type (total body irradiation [TBI] vs high-dose chemotherapy only). The estimated 10-year cumulative incidence of subsequent neoplasms was 4% (95% confidence interval [CI], 2%-6%); 10-year cumulative incidence of nonmalignant late effects included gonadal dysfunction (10%; 95% CI, 8%-13%), cataracts (10%; 95% CI, 7%-13%), avascular necrosis (8%; 95% CI, 5%-10%), diabetes mellitus (5%; 95% CI, 3%-7%), and hypothyroidism (3%; 95% CI, 2%-5%). Receipt of TBI was independently associated with a higher risk of cataracts only (hazard ratio [HR], 4.98; $P < .0001$) whereas chronic graft-versus-host disease (cGVHD) was associated with an increased risk of cataracts (HR, 3.22; $P = .0006$), avascular necrosis (HR, 2.49; $P = .006$), and diabetes mellitus (HR, 3.36; $P = .03$). Estimated 10-year overall survival and leukemia-free survival were 73% and 70%, respectively, and did not differ on the basis of conditioning type. In conclusion, late effects among survivors of MAC HCT for AYA AML are frequent and are more closely linked to cGVHD than type of conditioning.

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The full-text version of this article contains a data supplement.

Introduction

More than 50% of adolescents and young adults (AYAs)[1] with high-risk acute myeloid leukemia (AML) will transition to long-term survivorship after allogeneic hematopoietic cell transplantation (allo-HCT), with a rising prevalence of AYA transplant survivors anticipated in the coming years.[2] There is a heightened need to understand late effects and survivorship issues in this population because of the unique physiological and/or psychosocial challenges associated with the AYA life stages.[3] For example, relative to survivors of childhood and older adult cancer, the incidence of corticosteroid-associated avascular necrosis (AVN) peaks in AYA survivors, as does the likelihood of developing a subsequent neoplasm (SN).[4,5] Furthermore, late effects after HCT may have a disproportionately negative effect on the ability of AYA survivors to complete schooling, enter or re-enter the workforce, and/or bear children.[6] Survivorship challenges may be underestimated in this transplant population because of the high probability of AYAs terminating follow-up at transplant centers after HCT.[7]

The use of HCT is frequently necessary in AYA AML to achieve leukemia cure.[8-11] High-dose total body irradiation (TBI) in combination with chemotherapy or high-dose chemotherapy-only regimens have been the two most common myeloablative conditioning (MAC) approaches used in HCT for AYA AML. Studies of childhood HCT survivors demonstrate the potential for certain malignant health conditions related to these transplant exposures, and reports in adults and children suggest that high-dose TBI increases the risk of SNs after HCT.[12-15] Less is known about the impact of high-dose TBI or chemotherapy-only MAC regimens on nonmalignant late effects. Furthermore, there is a paucity of literature describing late effects in survivors of MAC HCT for AYA AML.

We therefore conducted a population-based study using data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) to identify the cumulative incidence of malignant and nonmalignant late effects, long-term survival, and risk factors for late effects and mortality in AYA AML survivors of HCT. We also sought to evaluate the impact of TBI-based vs chemotherapy-only MAC on the development of late effects and to determine any associations between type of conditioning regimen and survival.

Materials and methods

Data source

The CIBMTR is a research collaboration between the National Marrow Donor Program/Be The Match and the Medical College of Wisconsin. More than 450 transplantation centers worldwide contribute detailed data prospectively on consecutive transplantations to the CIBMTR. Compliance and accuracy of data reported to the CIBMTR are monitored by on-site audits. All patients are observed longitudinally until death or loss to follow-up. Patients and/or guardians provide written informed consent for data submission and research participation. The Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Patient population

AYA patients (age 15-39 years) with AML who underwent first HCT from an HLA-identical sibling (matched related donor) or matched (8/8) unrelated donor between 2000 and 2014, who remained disease free for at least 12 months after HCT, and who were reported to the CIBMTR were included. Patients received HCT conditioning with myeloablative TBI (≥500 cGy single dose or ≥800 cGy fractionated) or myeloablative doses of chemotherapy-only regimens (busulfan >8 mg/kg orally or the IV equivalent or melphalan >150 mg/m^2).[16] Exclusion criteria applied to patients who had received previous autologous HCT or allo-HCT, had a diagnosis of therapy-related AML or a cancer predisposition syndrome, or had relapsed and/or died within the first year after HCT. Patients for whom the CIBMTR team follow-up completeness index was less than 80% at 3 years after HCT were also excluded (n = 499).

Late effects and definitions of outcomes

Late effects data are collected through CIBMTR comprehensive report forms that were obtained on a subset of CIBMTR participants selected by weighted randomization for more comprehensive research-level data collection. Transplant centers reported the following late effects using a dichotomized response choice (yes/no) and the date of diagnosis of the late effect if applicable: congestive heart failure (ejection fraction <40%), myocardial infarction, seizure, stroke, cataracts, AVN, diabetes mellitus/hyperglycemia, hypothyroidism, growth hormone deficiency or growth disturbance, gonadal dysfunction or infertility requiring hormone replacement, hemorrhagic cystitis, pancreatitis, thrombotic microangiopathy or hemolytic uremic syndrome, veno-occlusive disease or sinusoidal obstruction syndrome, cirrhosis, renal failure requiring dialysis, bronchiolitis obliterans, cryptogenic organizing pneumonia, diffuse alveolar hemorrhage, noninfectious interstitial pneumonitis or idiopathic pneumonia syndrome, and SNs.

Overall survival (OS) was defined as the time from HCT until death as a result of any cause, and leukemia-free survival (LFS) was defined as the time until disease relapse or death. Patients who were alive without such events were censored at the time of last follow-up. Nonrelapse mortality (NRM) was defined as death in the absence of disease relapse or progression from the time of HCT. The primary cause of death for each patient was reported by the treating center.

Statistical analysis

The primary objectives of this study were to describe the cumulative incidence of late effects among AYA AML survivors of HCT and to compare late effects between patients with MAC TBI vs MAC chemotherapy only. Secondary objectives were to compare the prevalence of individual late effects and survival between the 2 groups and determine predictors of late effects, OS, LFS, relapse, and NRM among the total population.

Categorical variables were summarized by using standard descriptive measures. χ^2 test and Wilcoxon rank sum tests were used to compare the distribution of categorical variables and continuous variables, respectively. Late effects were categorized as SNs or as nonmalignant and were then summarized and individually analyzed. A pathology report was used to verify SNs whenever possible. The prevalence of each late effect among 2-, 5-, and 10-year survivors of HCT was computed. The cumulative incidence probability of an individual late effect at 2, 5 and 10 years after HCT was estimated, and death was treated as a competing risk for the whole group and for patients with TBI-based conditioning vs chemotherapy-only

conditioning. The cumulative incidence probability of NRM and relapse was estimated at 2, 5, and 10 years after HCT, with relapse and NRM treated as competing risks, respectively. The Kaplan-Meier method was used to estimate the probability of OS and LFS. Gray's test and log-rank test were used to compare cumulative incidence functions and survival functions, respectively, between the 2 treatment groups.

A Cox proportional hazards regression model was used to assess the impact of myeloablative TBI or chemotherapy only on individual late effects with a sufficient number of events (at least 5 late effects in each of the 2 treatment groups). Conditioning type was the main effect and additional variables were related to the patient (age, sex, race/ethnicity, cytomegalovirus serostatus), disease (disease status at HCT, time from diagnosis to HCT), in vivo T-cell depletion (antithymocyte globulin/alemtuzumab), year of HCT, and having chronic graft-versus-host disease (cGVHD) within 12 months of HCT. Stepwise selection was used to identify covariates to be included in the final models; all covariates associated with outcome at $P < .05$ were retained in the final models and were considered significant. Proportionality assumptions were checked for all variables considered. Time-dependent covariates were used in case non-proportionality was detected.

A similar Cox regression model was used to predict OS, LFS, NRM, and relapse. cGVHD and late effects were added into the regression model as time-dependent covariates. In addition to the variables used in the late effects analyses, Karnofsky score, donor type, and graft source were included. Patients without an event were censored at the last research-level follow-up date. All statistical analyses were performed using SAS 9.4 software.

The risk of cancer in the study cohort was compared with that of the general population using methods described in previous CIBMTR studies.[12,17,18] Briefly, for each transplant recipient, the number of person-years at risk was calculated from the date of transplantation until date of last contact, death, or diagnosis of new cancer, whichever occurred first. Incidence rates for all cancers in the general population were obtained from selected registries.[19] Age-, sex-, and region-specific cancer incidence rates were applied to the appropriate person-years at risk to compute the expected numbers of cancers. Observed-to-expected ratios (also called standardized incidence ratios) were calculated and the exact Poisson distribution was used to calculate 95% confidence intervals (CIs).[18]

Results

Patient characteristics

In all, 826 AYAs with AML (n = 390 [47%] receiving TBI; n = 436 [53%] receiving chemotherapy-only conditioning) who survived at least 1 year disease-free after MAC HCT were included. Baseline patient demographics and transplant characteristics stratified by TBI vs chemotherapy-only conditioning are described in Table 1. The median follow-up of survivors in the population was 77 months (range, 12-194 months); median follow-up was longer in the TBI group (94 months) relative to the chemotherapy-only group (73 months). The majority (n = 367 [94%]) of those included in the TBI group received TBI doses ≥1200 cGy; the most commonly used myeloablative chemotherapy regimen was busulfan with cyclophosphamide (n = 311 [71%]). Of the patients who were treated with busulfan-based chemotherapy, 156 (30%) received their dose by the oral route and 353 (68%) received their dose IV. Grades 2 to 4 acute GVHD (aGVHD) occurred in 36% of the patients overall, and grades 3 to 4 aGVHD occurred in 9% of patients receiving either TBI or non-TBI–based conditioning (Table 2). cGVHD occurred in 55% of the total study cohort, with extensive cGVHD documented in 45% of those receiving TBI and 44% of those receiving non-TBI–based conditioning. At the time of analysis, 177 deaths (21%) had occurred in the total population, with primary disease representing the most common cause of death in both groups.

SNs

An SN was reported in 2% (n = 16) of evaluable AYA AML survivors (supplemental Table 1). Solid cancers accounted for 15 of the 16 SNs; skin cancer was the most prevalent (1 melanoma and 7 non-melanoma skin cancers). The estimated 2-, 5-, and 10-year cumulative incidence of SNs was 0% (95% CI, 0%-1%), 1% (95% CI, 0%-2%), and 4% (95% CI, 2%-6%), respectively (Table 3). There was no difference in the estimated 10-year cumulative incidence of SNs after stratifying for age (15-19 years, 20-29 years, and 30-39 years) (supplemental Table 2). Overall, the estimated 10-year cumulative incidence of SNs did not significantly differ based upon conditioning therapy type (3% for TBI-based vs 4% for chemotherapy-only conditioning; $P = .73$). Multivariable analysis demonstrated that the type of conditioning regimen was not associated with SNs; however, achieving a second or greater complete remission (CR2+) at the time of transplant was a risk factor for an SN compared with undergoing HCT in the first CR (CR1) (hazard ratio [HR], 2.70; 95% CI, 1.00-7.27; $P = .049$) (Table 4). Seven patients (44%) with SNs died; death as a result of the SN occurred in 1 patient (supplemental Table 3).

Nonmalignant late effects

Among the total population, 22% of AYA survivors reported at least 1 nonmalignant late effect (supplemental Table 4) with a higher frequency of 1 late effect (22% vs 12%) and ≥2 late effects (7% vs 3%) reported in patients exposed to TBI relative to chemotherapy-only MAC. The estimated cumulative incidence of nonmalignant late effects increased over 10 years (Table 3), particularly for cataracts, gonadal dysfunction, and AVN in which the estimated cumulative incidence was ≤4% at 2 years and approached 10% at 10 years. There was no difference in the estimated 10-year cumulative incidence of any nonmalignant late effect between younger and older AYAs (supplemental Table 2). Multivariable analyses of individual late effects demonstrated that TBI-based conditioning was significantly associated only with the development of cataracts (HR, 4.98; 95% CI, 2.42-10.24; $P < .001$) (Table 4). cGVHD at 1 year after HCT was independently associated with a greater risk of AVN (HR, 2.49; 95% CI, 1.29-4.76; $P = .006$), cataracts (HR, 3.22; 95% CI, 1.65-6.29; $P = .0006$), and diabetes mellitus (HR, 3.36; 95% CI, 1.12-10.04; $P = .030$). Female patients were more likely to have gonadal dysfunction compared with males (HR, 1.83; 95% CI, 1.10-3.04; $P = .019$). Disease status (CR2+ vs CR1) was significantly associated with a higher risk of cataracts (HR, 1.74; 95% CI, 1.00-3.03; $P = .049$) and gonadal dysfunction (HR, 2.02; 95% CI, 1.22-3.35; $P = .006$).

Survival outcomes

Unadjusted survival outcomes are described in Table 5. NRM at 10 years among the total population was 14% (95% CI,

Table 1. Baseline characteristics of patients undergoing first myeloablative HCT for AML at age 15-39 years between 2000-2014 who survived disease free for 12+ months (reported to the CIBMTR)

	All Patients				TBI				Chemotherapy only			
Variable	**No.**	**%**	**Median**	**Range**	**No.**	**%**	**Median**	**Range**	**No.**	**%**	**Median**	**Range**
No. of patients	826				390				436			
No. of centers	147				92				113			
Follow-up of survivors, mo			77	12-194			94	13-194			73	12-182
Year of transplant												
2000-2004	257	31			133	34			124	28		
2005-2009	359	43			180	46			179	41		
2010-2014	210	25			77	20			133	31		
Patient age at transplant, y			29	15-40			30	15-40			28	15-40
15-19	127	15			52	13			75	17		
20-29	325	39			151	39			174	40		
30-39	374	45			187	48			187	43		
Patient age at last contact/death, y			35	17-55			36	17-55			34	17-53
15-19	24	3			12	3			12	3		
20-29	221	27			85	22			136	31		
30-39	350	42			173	44			177	41		
40+	231	28			120	31			111	25		
Sex												
Male	449	54			213	55			236	54		
Female	377	46			177	45			200	46		
Race/ethnicity												
White	654	79			296	76			358	82		
Black/African American	18	2			7	2			11	3		
Hispanic	63	8			27	7			36	8		
Other*	81	10			56	14			25	6		
Performance score												
90-100	624	76			290	74			334	77		
<90	182	22			87	22			95	22		
Disease status before transplant												
CR1	576	70			267	68			309	71		
CR2+	250	30			123	32			127	29		
Cytogenetics												
Favorable	124	15			58	15			66	15		
Intermediate	502	61			231	59			271	62		
Unfavorable	148	18			76	19			72	17		
Donor												
HLA-identical sibling	362	44			158	41			204	47		
Matched (8/8) unrelated donor	464	56			232	59			232	53		
Graft type												
Bone marrow	294	36			140	36			154	35		
Peripheral blood	532	64			250	64			282	65		
Conditioning regimen												
TBI + cyclophosphamide	355	43			355	91			NA			
TBI + cyclophosphamide + etoposide	17	2			17	4			NA			
TBI + etoposide	18	2			18	5			NA			
Busulfan + cyclophosphamide	311	38			NA				311	71		
Busulfan + fludarabine	125	15			NA				125	29		

*Multiple races (n = 11), Asian (n = 61), American Indian or Alaska Native (n = 4), Native Hawaiian or Pacific Islander (n = 3), other unspecified (n = 2).

Table 1. (continued)

Variable	All Patients				TBI				Chemotherapy only			
	No.	%	Median	Range	No.	%	Median	Range	No.	%	Median	Range
Total TBI dose (cGy)			1200	550-1440			1200	550-1440	NA			
550-799	9	1			9	2			NA			
800-1199	14	2			14	4			NA			
≥1200	367	44			367	94			NA			
Busulfan route												
Oral	156	30			NA				156	30		
IV	353	68			NA				353	68		
Corticosteroids as part of GVHD prophylaxis												
No	760	92			353	91			407	93		
Yes	64	8			35	9			29	7		
Antithymocyte globulin/alemtuzumab before transplant												
No	688	83			356	91			332	76		
Yes	138	17			34	9			104	24		

*Multiple races (n = 11), Asian (n = 61), American Indian or Alaska Native (n = 4), Native Hawaiian or Pacific Islander (n = 3), other unspecified (n = 2).

11%-17%) and did not significantly differ based upon conditioning type. The cumulative incidence of relapse at 10 years was significantly lower in patients receiving TBI vs chemotherapy (13% vs 19%; $P = .01$); however, this did not translate into differences in LFS or OS between the conditioning groups.

Multivariable analyses (Table 6) revealed that the presence of cGVHD at 1 year after HCT (HR, 1.62; 95% CI, 1.19-2.21; $P < .002$) and development of SNs (HR, 7.97; 95% CI, 3.62-17.53; $P < .0001$) were associated with increased mortality.

Table 2. Posttransplant characteristics of patients undergoing first myeloablative HCT for AML at age 15-39 years between 2000-2014 who survived disease free for 12+ months (reported to the CIBMTR)

Variable	All patients		TBI		Chemotherapy only	
	No.	%	No.	%	No.	%
No. of patients	826		390		436	
aGVHD grade						
0	354	43	138	35	216	50
1	163	20	82	21	81	19
2	223	27	127	33	96	22
3	68	8	33	8	35	8
4	10	1	5	1	5	1
Maximum grade of cGVHD						
None	371	45	178	46	193	44
Limited	87	11	35	9	52	12
Extensive	367	44	177	45	190	44
Reported cause of death						
Total deaths	177	21	92	24	85	19
Primary disease	68	8	33	8	35	8
GVHD	28	3	18	5	10	2
Infection	22	3	12	3	10	2
IPn/ARDS	5	<1	3	<1	2	<1
Organ failure	19	2	8	2	11	3
SN	1	<1	0		1	<1
Other cause	21	3	10	3	11	3

ARDS, acute respiratory distress syndrome; IPn, interstitial pneumonitis.

Table 3. Estimated cumulative incidence of select late effects for AYA patients with AML after ablative HCT

Late effect	All patients (N = 826)		TBI (n = 390)		Chemotherapy only (n = 436)		P*
	No.	95% CI	No.	95% CI	No.	95% CI	
SNs							.73
2-y	0	0-1	0	0-1	0	0-1	
5-y	1	0-2	1	0-2	1	0-2	
10-y	4	2-6	3	1-7	4	1-8	
AVN							.2
2-y	2	1-4	3	2-5	2	1-3	
5-y	5	4-7	7	4-9	4	3-7	
10-y	8	5-10	9	6-13	6	4-9	
Cataracts							<.001
2-y	1	0-1	1	0-3	0	0-1	
5-y	5	3-7	8	6-12	1	0-2	
10-y	10	7-13	15	11-19	5	2-10	
Diabetes mellitus							.21
2-y	1	1-2	3	1-5	0	0-1	
5-y	3	2-4	4	2-6	2	1-4	
10-y	5	3-7	5	3-9	4	1-8	
Hypothyroidism							.38
2-y	1	0-1	1	0-2	0	0-1	
5-y	2	1-3	2	1-4	2	1-3	
10-y	3	2-5	4	2-7	3	1-5	
Gonadal dysfunction							.98
2-y	4	2-5	4	2-6	3	2-5	
5-y	7	5-9	7	5-10	6	4-9	
10-y	10	8-13	10	6-13	11	7-16	

*P value for comparison of TBI and chemotherapy-only MAC regimen.

Discussion

This population-based report is among the first to describe the burden of late effects and SNs in survivors of AYA AML. By using data reported to the CIBMTR on AYA AML patients who underwent HCT between 2000 and 2014, we were able to report the estimated cumulative incidence over time of developing a host of chronic health conditions. We also report that 4% of AYA survivors are estimated to develop an SN at 10 years. These data are important because data on late effects for AYA patients are lacking, thus hampering the development of evidence-based AYA-focused survivorship guidelines and SN monitoring.

For AYA AML patients undergoing HCT, a MAC regimen consisting of high-dose TBI or high-dose chemotherapy alone followed by HCT is considered standard of care.[11] Although there has not been a modern prospective randomized study comparing the 2 regimens in AYA AML, retrospective and observational reports demonstrate at least equivalent outcomes, if not superiority of non-TBI–based approaches for AML.[20-22] This equipoise provides a strong rationale for studying the late effects in young adults receiving these regimens and may provide additional support in favor of one conditioning type over another. However, in this study cohort of AYAs who had survived disease-free for at least 1 year after HCT, we did not find many significant differences in late effects based upon the type of conditioning regimen. Specifically, we found that although the prevalence of 1 or more late effects was greater in AYAs who received TBI, the estimated cumulative incidences of late effects and SNs were not significantly associated with type of conditioning regimen, with the exception of the development of cataracts, which were more likely to develop after TBI (HR, 4.98; $P < .001$).

Among the AYA HCT survivors included in our cohort, the estimated 10-year cumulative incidence of SNs was 4% (95% CI, 2%-6%), representing a threefold increase in the rate of malignancy compared with that in the healthy AYA population.[19] There was no significant difference in incidence of SNs by exposure to myeloablative TBI vs high-dose chemotherapy-based regimens. Although it is generally believed that the development of SNs is higher in patients conditioned with high-dose TBI, the literature is inconclusive because some studies that included AYA patients have demonstrated similar rates of SN development regardless of the conditioning regimen backbone, whereas others have shown that high-dose TBI leads to greater SN development.[12,14,17,23-29] In an evaluation of children and adults with AML in CR1 who were undergoing non-TBI–based MAC HCT, Majhail et al[30] reported a 10-year cumulative incidence of solid SNs of 1.2%, although only

Table 4. Multivariate Cox models for individual late effects in AYA patients with AML after ablative HCT

Late effect/variable	n	HR	95% CI	*P*
SN				
Conditioning regimen				.696
Non-TBI MAC	435	1		
TBI MAC	383	0.82	0.31-2.20	
Disease status at HCT				.049
CR1	571	1		
CR2+	247	2.70	1.00-7.27	
cGVHD				
No	368	1		
Yes	450	1.28	0.46-3.55	.637
AVN				
Conditioning regimen				.178
Non-TBI MAC	422	1		
TBI MAC	367	1.48	0.84-2.64	
cGVHD				.006
No	354	1		
Yes	435	2.49	1.29-4.76	
Cataracts				
Conditioning regimen				
Non-TBI MAC	432	1		
TBI MAC	379	4.98	2.42-10.24	<.0001
TBI MAC 550-1200 cGy	23	2.08	0.26-16.45	.486
TBI MAC ≥1200 cGy	356	5.16	2.51-10.63	<.0001
Disease status at HCT				.049
CR1	567	1		
CR2+	244	1.74	1.00-3.03	
cGVHD				.0006
No	363	1		
Yes	448	3.22	1.65-6.29	
Diabetes mellitus				
Conditioning regimen				.202
Non-TBI MAC	340	1		
TBI MAC	314	1.82	0.72-4.58	
cGVHD				.030
No	300	1		
Yes	354	3.36	1.12-10.04	
Gonadal dysfunction				
Conditioning regimen				.980
Non-TBI MAC	419	1		
TBI MAC	365	0.99	0.60-1.64	
Sex of recipient				.019
Male	437	1		
Female	347	1.83	1.10-3.04	
Disease status before HCT				.006
CR1	544	1		
CR2+	240	2.02	1.22-3.35	
Hypothyroidism				
Conditioning regimen				.367
Non-TBI MAC	426	1		
TBI MAC	372	1.55	0.60-4.00	

half the patients in the study population were AYAs. In a recent large analysis of SNs after HCT performed at a single institution, Baker et al[14] showed that the 20-year cumulative incidence of SNs in the AYA age range was 13.5% (95% CI, 11.8%-15%) and that use of a TBI dose of >450 cGy as part of conditioning was independently associated with SNs.

This study had more extensive follow-up than most other studies reported in the transplant literature, and the findings are particularly concerning because the estimated incidence of SNs continued to rise substantially in every decade after HCT. Although we did not find a difference in SNs based upon type of conditioning, our median follow-up time was shorter (~8 years for the TBI-exposed cohort), and the latency period for radiogenic cancers can be much longer.[31,32] Our study also showed an increased risk of SNs among patients achieving CR2+ at the time of transplant. This finding suggests that patients who receive additional therapies to obtain disease remission before transplant may need more vigorous surveillance for SNs. Our findings, in combination with those from other reports, suggest that the incidence of SNs for AYAs after HCT are not trivial, and life-long monitoring for SNs (including skin cancer) is necessary for this group of patients who are otherwise cured of their original disease and have many potential years of personal and societal productivity.

The cumulative incidence of nonmalignant late effects increased over time in this AYA AML survivor cohort. In particular, the estimated 10-year cumulative incidence of cataracts (10%) and AVN (8%) are alarming in this population of young adult survivors. Similar rates of AVN may be seen after use of steroid therapy in AYA acute lymphocytic leukemia; however, non-HCT–based treatments for AML rarely incorporate steroids or other agents known to predispose for AVN. Similarly, the substantial risk of developing cataracts in this young cohort suggests that early screening may be appropriate for survivors of AYA HCT. Unsurprisingly, the presence of cGVHD was linked to these late effects and to diabetes mellitus, likely because of the higher use of long-term corticosteroids by these patients. These findings underscore the importance of developing curative HCT platforms that do not result in cGVHD and also highlight the need for ongoing comprehensive long-term follow-up in AYA survivors with a history of cGVHD. Because patients in this age group are often late to report symptoms and may be less adherent to long-term follow-up care after HCT,[7,33] these are areas that would benefit from further AYA-focused interventional research.[34] Finally, the prevalence of gonadal dysfunction requiring hormone replacement was 7%, which is much lower compared with that in other studies of patients from childhood to adulthood.[35,36] Gonadal dysfunction, an important issue for AYA survivors because of its impact on reproductive potential, may be difficult to capture via the current reporting method; this will likely be improved by the routine use of population-based quality-of-life and patient-centered surveys and measures after HCT as proposed by the CIBMTR.[37]

Table 5. Unadjusted survival estimates of AYAs with AML who survived at least 1 year disease free after ablative HCT

Outcomes	All patients (N = 826) Probability	95% CI	TBI (n = 390) Probability	95% CI	Chemotherapy only (n = 436) Probability	95% CI	P*
OS							.47
2-y	93	92-95	92	90-95	94	92-96	
5-y	81	78-84	80	76-84	83	79-86	
10-y	73	69-76	72	66-77	73	67-79	
Relapse							.01
2-y	8	6-10	6	4-8	10	8-13	
5-y	15	13-18	12	9-16	18	15-22	
10-y	17	14-19	13	10-17	19	16-23	
NRM							.09
2-y	3	2-5	5	3-7	2	1-4	
5-y	9	7-12	11	8-15	8	5-10	
10-y	14	11-17	16	12-21	11	7-15	
LFS							.40
2-y	88	86-91	90	86-92	87	84-90	
5-y	75	72-78	77	72-81	74	70-78	
10-y	70	66-74	70	65-76	70	65-75	

*P value for comparison of TBI vs chemotherapy-only MAC regimen.

Table 6. Multivariable analyses of survival outcomes of AYAs with AML who survived at least 1 year disease free after HCT

Outcome/variable	n	HR	95% CI	P
OS				
Conditioning regimen				.541
Non-TBI MAC	436	1		
TBI MAC	390	1.10	0.82-1.48	
cGVHD				.002
No	371	1		
Yes	455	1.62	1.19-2.21	
SN				<.0001
No	810	1		
Yes	16	7.97	3.62-17.53	
Relapse				
Conditioning regimen				.02
Non-TBI MAC	436	1		
TBI MAC	390	0.65	0.45-0.94	
NRM				
Conditioning regimen				.238
Non-TBI MAC	436	1		
TBI MAC	390	1.29	0.85-1.97	
cGVHD				<.0001
No	371	1		
Yes	455	3.39	2.01-5.72	
Donor				.001
HLA-identical sibling	362	1		
8/8 MUD	464	2.16	1.35-3.45	
SN				<.0001
No	810	1		
Yes	16	14.57	5.78-36.75	
LFS				
Conditioning regimen				.347
Non-TBI MAC	436	1		
TBI MAC	390	0.88	0.67-1.15	
cGVHD				.006
No	371	1		
Yes	455	1.47	1.11-1.95	
SN				<.0001
No	810	1		
Yes	16	9.09	4.12-20.02	

URD, unrelated donor.

Ten-year estimated OS was 73% and estimated LFS was 70% for AYA AML patients who survived disease-free for at least 1 year after HCT. Similar to other observational studies performed across a range of patient ages,[20-22] long-term survival estimates in our study did not differ based upon whether patients received TBI or a chemotherapy-only conditioning regimen. However, the estimated 10-year cumulative incidence of NRM of 14% again suggests that AYAs require ongoing medical care beyond 1 year after HCT. Furthermore, late relapse remains an issue as evidenced by a 15% cumulative incidence of relapse at 5 years. Fortunately, very late relapses (beyond 5 years) seem to be rare events. Consistent with other studies of HCT survivors,[38,39] AML relapse was identified as the leading cause of death in our cohort, underscoring the importance of relapse prevention strategies after HCT.

Although all retrospective studies have inherent limitations, studying late effects after HCT raises important challenges. First, the prevalence of late effects reported in our cohort was lower than expected. For example, we found a 10-year cumulative incidence of cataracts of 15% (95% CI, 11%-19%) for patients exposed to TBI, whereas other studies in children and adults have reported rates of 30% to 70% for cataract development at 10 years after transplant for patients exposed to fractionated TBI.[40-42] However, it is possible that technological advances in radiotherapy techniques beginning in the year 2000 may have contributed to less ocular toxicity in recent years. Similarly, as mentioned earlier, the low rate of gonadal dysfunction reported in this cohort was quite low. Our findings, therefore, likely reflect an underestimation of the true burden of late complications after HCT for AYA AML. It is unclear whether potential underreporting may be a result of inconsistent follow-up at the HCT center level or a result of the evolving late effects collection methods used by the CIBMTR over time. Future efforts aimed at improving the ascertainment of late effects and SNs are currently ongoing through the recommendations provided by the American Society of Transplantation and Cellular Therapy Late Effects Task Force. Our study was also hampered by the relatively short median follow-up time of survivors after HCT. It is well known that certain late complications, including late cardiac events[43] and SNs appear years, and even decades, after HCT.[17,23] Our cohort included patients who received transplants as recently as 2014, which

potentially affected our ability to capture late effects commonly occurring many years after HCT; however, we believe that evaluation of late effects that occur early in the disease process, potentially occurring as soon as 1 year after HCT, was important for understanding the full range of late effects and their time to development.

Finally, our study did not include survivors who developed disease relapse in the first year after HCT. Although some late effects may occur very early after HCT (eg, cataracts, infertility, hypothyroidism) and precede disease relapse, our rationale for excluding these patients was based upon the understanding that these patients have poor survival after early relapse and/or they received additional intensive therapies that may influence the development of late effects and confound the primary exposure-outcome relationship.

We acknowledge the difficulties related to studying late effects in this population, and we believe that our study provides meaningful data to the nascent literature regarding late effects in AYA AML. The development of cataracts seems to be associated with TBI-based conditioning; however, other late effects, including SNs, cannot be clearly linked to TBI in our AYA cohort. Systematic ascertainment of late effects in AYAs is critically necessary for developing AYA-focused survivorship guidelines and care plans, as has been done for survivors of childhood cancers. The HCT community is poised to conduct the studies that will further the understanding of late complications in AYAs and improve the care of this important population of cancer survivors.

Authorship

Contribution: C.J.L., L.S.M., and B.E.S. designed, directed, and performed research, analyzed data, and wrote the manuscript; H.R.T., R.P., and S.B.-S. provided data sets for analysis; H.R.T., S.B.-S., S.K., and R.B. performed statistical analysis; B.E.S., D.B., and B.K.H. reviewed data and the manuscript; and M.B., N.S.M., H.M.L., P.J.S., D.I.M., M.R.L., S.C., Y.I., Z.D., G.C.H., R.F.O., K.A.K., J.L.L., S.J.R., S.M.B., N.S.B., J.A.Y., K.M.P., M.L.A., M.K., N.F., S.S., P.H., C.O.F., A.R., S.G., S.N., and L.B. critically reviewed the data and approved the final manuscript before it was submitted.

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