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CME Article

Subsequent malignant neoplasms among children with Hodgkin lymphoma: a report from the Children's Oncology Group

Lisa Giulino-Roth,[1] Qinglin Pei,[2,3] Allen Buxton,[4] Rizvan Bush,[4] Yue Wu,[2] Suzanne L. Wolden,[5] Louis S. Constine,[6,7] Kara M. Kelly,[8,9] Cindy L. Schwartz,[10] and Debra L. Friedman[11,12]

[1]Department of Pediatrics, Weill Cornell Medical College, New York, NY; [2]Department of Biostatistics, University of Florida, Gainesville, FL; [3]Children's Oncology Group Statistics and Data Center, Gainesville, FL; [4]Children's Oncology Group Statistics and Data Center, Monrovia, CA; [5]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY; [6]Department of Radiation Oncology and [7]Department of Pediatrics, James P. Wilmot Cancer Institute, University of Rochester, Rochester, NY; [8]Department of Pediatrics, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY; [9]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [10]Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI; [11]Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN; and [12]Vanderbilt-Ingram Cancer Center, Nashville, TN

KEY POINTS

- **Among 1711 children with HL treated on the COG AHOD0031 trial, the 10-year cumulative incidence of subsequent malignancy is 1.32%.**
- **The 10-year cumulative incidence of secondary MDS/AML is 0.2%, which is similar to that observed with other HL therapies.**

Survivors of Hodgkin lymphoma (HL) have an increased risk of subsequent malignant neoplasms (SMNs). Response-adapted treatment may decrease this risk by reducing exposure to therapy associated with SMN risk. The Children's Oncology Group study AHOD0031 evaluated response-adapted therapy for children and adolescents with intermediate-risk HL. We report the SMNs among 1711 patients enrolled in AHOD0031. Patients were treated with 4 cycles of doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide with or without involved-field radiation therapy (RT). Patients with a slow early response to initial chemotherapy were randomized to 2 additional cycles of dexamethasone, etoposide, cisplatin and cytarabine or no additional chemotherapy, and all received RT. At a median follow-up of 7.3 years, an analysis of SMNs was performed. The 10-year cumulative incidence of SMN was 1.3% (95% confidence interval [CI], 0.6-2.0). SMNs included 3 patients with acute myeloid leukemia (AML), 11 with solid tumors, and 3 with non-Hodgkin lymphoma. Sixteen of 17 patients with an SMN had received combined modality therapy. The standardized incidence ratio for SMN was 9.5 (95% CI, 4.5-15.2) with an excess absolute risk of 1.2 per 1000 person-years. The cumulative incidence of SMNs was higher among patients who received RT ($P = .037$). In multivariate analysis, RT, B symptoms, and race were associated with SMN risk. Given the latency from exposure, we have likely captured all cases of secondary leukemia and myelodysplastic syndrome (MDS). Longer follow-up is needed to determine the risk of solid tumors. Avoidance of RT without sacrificing disease control should remain a goal for future therapeutic approaches. This trial was registered at www.clinicaltrials.gov as #NCT00025259. (*Blood*. 2021;137(11):1449-1456)

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Disclosures

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Learning objectives

Upon completion of this activity, participants will be able to:

1. Describe incidence and characteristics of subsequent malignant neoplasms (SMNs) among children and adolescents who received response-adapted Hodgkin lymphoma (HL) treatment for newly diagnosed intermediate-risk HL in the Children's Oncology Group AHOD0031 trial
2. Determine risk factors for SMNs among children and adolescents who received response-adapted HL treatment for newly diagnosed intermediate-risk HL in the Children's Oncology Group AHOD0031 trial and updated outcomes from this trial
3. Identify the clinical implications of incidence, characteristics, and risk factors of SMNs among children and adolescents who received response-adapted HL treatment for newly diagnosed intermediate-risk HL in the Children's Oncology Group AHOD0031 trial, as well as of other updated outcomes

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Introduction

The outcome for children and adolescents with Hodgkin lymphoma (HL) treated with modern therapies is excellent, with event-free survival (EFS) now exceeding 85%.[1,2] Unfortunately, this high cure rate is accompanied by the cost of a potential risk for long-term toxicity that can diminish life expectancy and quality of life in survivors. Subsequent malignant neoplasms (SMNs) are among the most serious and life-threatening consequences of HL treatment. HL survivors are at increased risk for subsequent myelodysplastic syndrome (MDS), leukemia, sarcomas, breast cancer, thyroid cancer, and other malignancies.[3-7] The risk for MDS and leukemia is associated with exposure to alkylating agents and topoisomerase-II inhibitor chemotherapy,[8,9] with the greatest majority occurring within 10 years of exposure. Solid tumor risk is associated with exposure to radiation therapy (RT) and/or alkylating agents and increases in incidence over time without plateau.[10,11]

Response-adapted treatment approaches for HL seek to reduce long-term toxicity while maintaining high cure rates by reducing therapy in patients with a rapid response to initial therapy and/or escalating therapy in patients with a slow early response. The Children's Oncology Group study AHOD0031 was a response-adapted phase 3 trial conducted among children and adolescents with newly diagnosed intermediate-risk HL.[12] This study is the largest pediatric phase 3 HL trial reported to date and provides an opportunity to evaluate the risk of SMNs using a standard pediatric treatment backbone. Herein, we report updated outcomes from the AHOD0031 trial and the incidence and risk factors for SMNs among 1711 eligible patients enrolled on this study.

Patients and methods

Patients and treatment

The Children's Oncology Group study AHOD0031 enrolled 1734 children, adolescents, and young adults with newly diagnosed, intermediate-risk HL from 2002 to 2009. AHOD0031 was approved at the institutional review boards of all participating sites and conducted in accordance with the Declaration of Helsinki. Treatment consisted of response-based therapy using the doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide (ABVE-PC) chemotherapy backbone (supplemental Table 1, available on the *Blood* Web site). Patients with a rapid early response (RER) after 2 cycles of ABVE-PC and a complete response (CR) after 4 cycles were randomized to receive 21-Gy involved-field RT (IFRT) vs no further therapy. Patients with a slow early response (SER) to 2 cycles of ABVE-PC received a total of 4 cycles of ABVE-PC with or without an additional 2 cycles of dexamethasone, etoposide, cisplatin, and cytarabine (DECA; supplemental Table 2). All patients with a SER received IFRT. Given the time frame of this study, all patients treated with RT received photon-based therapy. Among the entire cohort, ~27% of patients were treated with chemotherapy alone. A consort diagram for this trial is provided in supplemental Figure 1.

At a median follow-up of 7.3 years, an ascertainment of SMNs was undertaken with relapse and death as competing events. To determine if solid tumor SMNs were in the field of RT, a review of RT planning was performed. Nonmelanoma skin cancers were excluded from this analysis. To analyze SMN risk in the context of treatment outcomes, we also conducted an updated analysis of EFS and overall survival (OS) in each treatment cohort.

Statistical analyses

To investigate the difference between patients with SMN and those without, χ^2 tests were used to compare categorical variables and Student *t* tests were used to compare continuous variables. Cumulative incidences of specified SMNs were calculated and compared across groups with K-sample tests. Cox multivariable regression was conducted to identify the significant factors associated with the risk of SMN. The final model removed covariates with *P* value >.2 with step-wise selection. The standardized incidence ratios (SIRs) and absolute excess risks (AERs) were calculated for each SMN subtype using Surveillance Epidemiology and End Results (SEER)

Table 1. Characteristics of patients enrolled on AHOD0031

Variable	All patients, n = 1711	No SMN, n = 1694	SMN, n = 17	*P*
Age at diagnosis, mean ± SD, y	14.5 ± 3.4	14.5 ± 3.3	13.8 ± 4.3	.35
Height, mean ± SD, cm	161.0 ± 18.1	161.1 ± 18.1	157.2 ± 24.3	.38
Weight, mean ± SD, kg	60.5 ± 21.9	60.6 ± 21.9	58.6 ± 25.3	.71
Erythrocyte sedimentation rate (mm/h)	49.7 ± 33.9	49.6 ± 33.9	58.3 ± 34.4	.63
Gender				.33
Male	907	896 (52.9)	11 (64.7)	
Female	804	798 (47.1)	6 (35.3)	
Race				.06
Asian	49	47 (2.8)	2 (11.8)	
Black	189	188 (11.1)	1 (5.9)	
White	1333	1322 (78.0)	11 (64.7)	
Other	140	137 (8.1)	3 (17.6)	
Ethnicity				.75
Non-Hispanic	1404	1390 (82.1)	14 (82.4)	
Hispanic	257	254 (15.0)	3 (17.6)	
Unknown	50	50 (2.9)		
Stage				.97
I	98	97 (5.7)	1 (5.9)	
II	1005	996 (58.8)	9 (52.9)	
III	354	350 (20.7)	4 (23.5)	
IV	254	251 (14.8)	3 (17.6)	
B symptoms				.17
No	1327	1317 (77.7)	10 (58.8)	
Yes	380	373 (22.1)	7 (41.2)	
Unknown	4	4 (0.2)		
Bulk disease				.11
No	435	427 (25.2)	8 (47.1)	
Yes	1256	1247 (73.6)	9 (52.9)	
Unknown	20	20 (1.2)		
Histology				.47
Lymph predominant	96	96 (5.7)		
Lymph depleted	4	4 (0.2)		
Nodular sclerosing	1383	1369 (80.8)	14 (82.4)	
Mixed cellularity	156	155 (9.1)	1 (5.9)	
Unknown	72	70 (4.1)	2 (11.8)	

Values represent n (%) of patients unless otherwise indicated.

program data for expected rates. Kaplan-Meier estimations were provided for both EFS and OS end points. Survival curves were compared with log-rank tests.

Results

Updated outcomes from AHOD0031

With the final 10-year follow-up for this trial now complete, we performed an updated analysis of EFS and OS among patients treated on AHOD0031. The 10-year EFS and OS among the entire cohort are 81.5% (95% confidence interval [CI], 78.1-84.8) and 96.1% (95% CI, 94.5-97.8), respectively. Among patients with a RER and CR who were randomized to receive RT vs no RT, the 10-year EFS is 83.8% vs 82.5%, respectively ($P = .260$) and the 10-year OS for RT vs no RT is 97.0% vs 97.3% ($P = .530$). Among patients with a SER, the 10-year EFS among those who were randomized to DECA vs no DECA is 78.8% vs 71.8% ($P = .178$); 10-year OS is 93.5% vs 91.8% ($P = .600$). In the original report of AHOD0031, there was a trend toward improved EFS among SER patients with a positive interim fluorodeoxyglucose positron emission tomography (FDG-PET) treated with DECA when compared with no DECA (4-year EFS 70.4% vs 54.6%, $P = .05$). The 10-year EFS among SERs with a positive interim FDG-PET treated with DECA vs no DECA is 69.1% vs 50.9% ($P = .16$), and the 10-year OS is 90.1% vs 79.6% ($P = .161$).

Table 2. Characteristics of solid tumor and lymphoma SMNs

SMN	Age at HL dx (y)	Gender	HL stage	Chemotherapy	RT	Time to SMN (y)	SMN site	SMN in RT field	Status
Solid tumors									
Embryonal carcinoma	18	M	IIIIA	ABVE-PC × 4	Y	1.6	Testis	N	Alive
Breast cancer	17	F	IB	ABVE-PC × 4 + DECAx2	Y	13.4	Breast	Y	Alive
Mucoepidermoid carcinoma	15	F	IVA	ABVE-PC × 4	Y	6.4	Parotid gland	Y*	Alive
Osteosarcoma	15	F	IIB	ABVE-PC × 4	Y	5.5	C3 vertebral body	Y	Alive
Papillary adenocarcinoma	9	M	IIIA	ABVE-PC × 4	Y	9.5	Thyroid	Y	Alive
Papillary adenocarcinoma	14	M	IIB	ABVE-PC × 4	Y	9.2	Thyroid	Y	Alive
Papillary adenocarcinoma	3	M	IIA	ABVE-PC × 4	Y	8.1	Thyroid	Y	Alive
Papillary adenocarcinoma	15	F	IIB	ABVE-PC × 4	Y	4.4	Thyroid	Y	Alive
Papillary adenocarcinoma	16	M	IIA	ABVE-PC x 4	Y	7.2	Thyroid	Y	Alive
Papillary adenocarcinoma	17	F	IIA	ABVE-PC × 4	Y	10.2	Thyroid	Y	Alive
Renal cell carcinoma	15	M	IIIA	ABVE-PC × 4	Y	13.6	Kidney	N†	Deceased
Lymphoma									
B-NHL	4	M	IIB	ABVE-PC × 4	N	4.2	Lacrimal gland	N	Alive
T-LL	14	M	IIIA	ABVE-PC × 4	Y	2.1	Mediastinum	Y	Deceased
Mycosis fungoides	16	M	IIB	ABVE-PC × 4	Y	6.6	Skin	Unknown	Alive

dx, diagnosis; F, female; M, male; N, no; T-LL, T-cell lymphoblastic lymphoma; Y, yes.

*Under partial block.

†Potential area of scatter.

Incidence and characteristics of subsequent neoplasms

Among 1711 patients, 17 SMNs occurred as a first event. The characteristics of the entire cohort are presented in Table 1 together with a comparison between patients who subsequently developed a SMN and those who did not. The median time to SMN was 6.4 years (range, 1.6-13.6 years). SMNs included 3 patients with secondary acute myeloid leukemia (AML), 11 with solid tumors, and 3 with non-Hodgkin Lymphoma (NHL). Sixteen of the 17 cases occurred in patients treated with ABVE-PC without DECA. There were an additional 4 SMNs that occurred as a second or greater event. This included 1 case of each of the following: papillary thyroid cancer, synovial sarcoma, myelodysplastic syndrome, and melanoma. These SMNs were not included in the subsequent analyses to focus on the risk conferred by AHOD0031 therapy alone.

Among the 3 cases of secondary AML, the median time to SMN was 2.0 years (range, 1.8-2.7 years). All 3 patients had received 4 cycles of ABVE-PC chemotherapy and RT. In 2 of 3 AML cases, a rearrangement was identified at the MLL locus. In the third case, tumor cytogenetics could not be obtained. All patients with secondary AML died of disease.

There were 3 cases of subsequent NHL: 1 case of B-cell NHL, 1 case of T-cell lymphoblastic lymphoma, and 1 case of mycosis fungoides. None of these patients had nodular lymphocyte predominant HL, which was confirmed by central pathology review. Two of the 3 patients who developed NHL had received RT, 1 of whom developed NHL in the RT field. The NHL SMNs occurred at a latency of 4.2, 2.1, and 6.6 years, respectively. The patient with T-cell lymphoblastic lymphoma died of disease; the other patients remain alive at last follow-up.

Among patients who developed a solid tumor, the median time to SMN was 8.1 years (range, 1.6-13.6 years). Tumors included 6 cases of papillary thyroid carcinoma and 1 each of the following: osteosarcoma of the C3 vertebrae, embryonal carcinoma of the testis, mucoepidermoid carcinoma of the parotid gland, renal cell carcinoma, and invasive breast cancer (Table 2). All patients who developed a solid tumor SMN had received radiation, and only 1 patient (with invasive breast cancer) had also received DECA. The SMN was located within the RT field in 9 of 11 cases. In addition, in the case of renal cell carcinoma, although the kidney was not in-field, this patient did receive RT to para-aortic lymph nodes with potential scatter to the kidneys. One case of embryonal carcinoma of the testis occurred outside of the RT field. Among the 11 cases of solid tumor SMNs, 1 patient died of disease (renal cell carcinoma); the others were alive at the time of last follow-up.

In total, the cumulative incidence of any SMN as a first event was 0.5% (95% CI, 0.1-0.8) at 5 years and 1.3% at 10 years (95% CI, 0.6-2.0) (Figure 1A). The 10-year cumulative incidences for secondary AML, NHL, and solid tumors were 0.2% (95% CI, 0-0.4), 0.16% (95% CI, 0-0.4), and 1.0% (95% CI, 0.3-1.6), respectively (Figure 1B-C). The 10-year cumulative incidence of papillary thyroid carcinoma was 0.64%. Patients exposed to RT had a higher cumulative incidence of SMNs compared with those who did not receive RT ($P = .037$; Figure 1D).

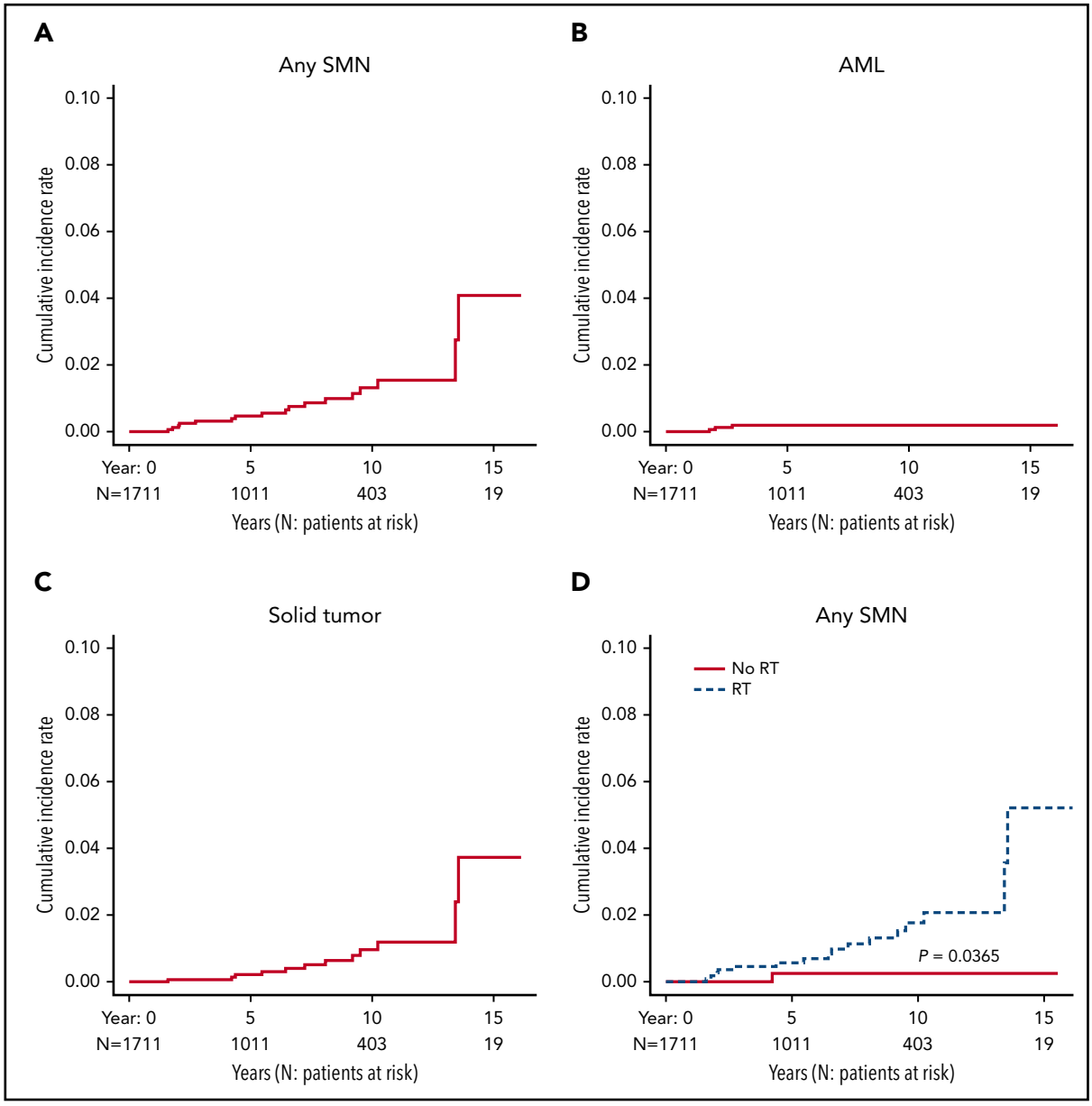

Figure 1. Cumulative incidence of SMNs. (A) Cumulative incidence of any SMN. (B) Cumulative incidence of AML. (C) Cumulative incidence of solid tumors. (D) Cumulative incidence of any SMN according to RT exposure.

Risk of subsequent neoplasms relative to the general population

To compare the risk of malignancy in our cohort to the general population, observed and expected numbers of malignancy by age, diagnosis, and site were calculated (Table 3). The SIR for any SMN is 9.5 (95% CI, 4.5-15.2) with an AER of 1.2 per 1000 person-years.

Risk factor analysis for subsequent neoplasms

To evaluate patient or disease factors which may have been associated with increased SMN risk, we performed univariate and multivariate analyses of potential risk factors. A Cox multivariable analysis was conducted considering the following: age at diagnosis, ESR, gender, race, ethnicity, stage, B symptoms, bulk disease, histology, and RT exposure. The final model was based on gender, race, B symptoms, bulk disease, and RT exposure, while all other covariates were removed because of large *P* value (>.2). In this model, race (Asian vs White: hazard ratio [HR], 7.8; 95% CI, 1.7-36.2; Black vs White: HR, 0.8; 95% CI, 0.1-5.; $P = .028$), B symptoms (HR, 3.1; 95% CI, 1.1-8.3; $P = .027$), and RT exposure (HR, 8.6; 95% CI, 1.1-66.9; $P = .040$) were each associated with risk for SMN.

Discussion

In this analysis, we report on the SMN risk from the largest phase 3 trial in pediatric HL reported to date. This work provides key information about the risks and benefits of contemporary therapy for HL and, specifically, the response-adapted treatment approach used in AHOD0031. Comparisons with other trials are limited due to different risk patient populations, time of follow-up, and variability in RT dose, field, and use. Our 10-year cumulative incidence of any

Table 3. SIR and AER of SMNs

Cancer diagnosis	Observed cases	Expected cases	SIR	95% CI	AER
Any SMN	17	1.79	9.5	4.5-15.2	1.2
Solid tumor within RT field*	10	0.1	105.1	83.2-193.4	0.8
MDS/AML	3	0.012	249.9	195.7-730.3	0.2
NHL	2	0.02	94.4	63.7-340.9	0.2
Osteosarcoma	1	0.068	14.7	5.5-81.9	0.1
Embryonal carcinoma	1	0.027	37.4	17.9-207.8	0.1
Papillary thyroid carcinoma	6	0.06	100.1	76.9-217.8	0.5
Mucoepidermoid carcinoma	1	0.008	119.4	68.1-664.5	0.1
Renal cell carcinoma	1	0.005	207.4	124.5-1153.7	0.1
Breast cancer	1	0	NA	NA	0.1

MDS, myelodysplastic syndromes; NA, not applicable.

*Solid tumors within the RT field for this cohort included osteosarcoma, papillary thyroid carcinoma, mucoepidermoid carcinoma, and breast cancer.

SMN of 1.3% is lower than that reported in the GPOH-HD95 trial, which enrolled 925 pediatric patients with HL and reported a 10-year CI of SMN of 3.1% ± 0.8%.[13] This response-adapted trial used the vincristine, etoposide or procarbazine, prednisone, and doxorubicin (OPPA/OEPA) ± cyclophosphamide, vincristine, prednisone, and procarbazine (COPP) chemotherapy backbone and spared RT in 18% of patients. In a recent report from the Childhood Cancer Survivor Study, the 15-year CI of SMN among pediatric cancer survivors treated in the 1990s was 1.5% (95% CI, 1.1-1.5).[14] This retrospective cohort study included 5-year survivors of any pediatric malignancy but would not include any deaths due to cancer prior to 5 years.

Our low 0.2% 10-year cumulative incidence of therapy-related AML is similar to the rates observed in the Pediatric Oncology Group 9426 and 9425 trials,[15] which used ABVE and ABVE-PC chemotherapy respectively, the GPOH-HD95 trial (0.1%)[13] and that observed in adults treated with ABVD (0.3%).[16] With a median follow-up of 7.3 years, we likely have captured the majority of therapy-related AML/myelodysplastic syndrome cases, as these typically occur within 5 to 10 years of exposure. All patients with secondary AML died of disease, highlighting the need to minimize this risk, which is associated with high fatality. Of note, none of the patients with therapy-related AML in our cohort received DECA, which is relevant, as excess risk for leukemia has been reported following treatment with etoposide and cisplatin.[17]

Eleven patients developed solid tumors in our cohort, including 6 cases of papillary thyroid carcinoma, all in the RT field. In contrast to other solid cancers where the SMN risk increases with higher RT doses, for papillary thyroid cancer, the risk increases with doses up to 20 Gy and then decreases with very few cases observed after exposure >40 Gy, possibly due to cell death.[6,18,19] Survivors on this trial treated with 21 Gy might therefore be expected to have higher rates of thyroid cancer than those treated with higher RT doses used in older regimens. The risk for papillary thyroid cancer is also higher among patients who received RT at <10 years of age.[20] Among the 6 patients who developed papillary thyroid cancer in our cohort, 2 were under the age of 10 years at time of treatment (9 and 3 years). Our data support regular screening for thyroid cancer among HL survivors exposed to neck RT. The Children's Oncology Group recommends an annual thyroid examination and, if palpable nodules are identified, an ultrasound evaluation with fine needle aspiration as clinically indicated.[21,22]

Breast cancer is commonly reported following HL treatment, particularly with use of RT.[3,4,6,7] Only 1 case of breast cancer, which occurred in the RT field at a latency of 13.4 years, is noted in our cohort, but the follow-up time for the development of breast cancer in is still short, and patients who received RT with breast tissue in the field remain at risk.[6,23-25] Based on this known risk, consensus guidelines recommend early breast cancer screening among childhood survivors of HL.[21] With longer follow-up, we will be able to evaluate whether the low-dose and reduced-field radiation used in AHOD0031 lowered risk in this cohort.

In our multivariate analysis of risk factors for SMNs, RT exposure, B symptoms, and Asian race were associated with risk for SMNs. The reasons for these associations, other than treatment with RT, remain unclear, and these associations have not previously been noted. Further follow-up with this cohort and in other cohorts is required to further evaluate these associations. Radiation exposure is well known to be associated with solid tumor SMNs. It is important to note that this trial used IFRT. Contemporary trials are using involved-node or involved-site RT, with fields considerably smaller than those used in this trial, and thus, risk to normal tissues may be reduced. Proton-based RT may also decrease risk.[26,27] Longer follow-up will be needed to determine if these changes in RT will further reduce the risk of solid tumor SMNs.

The updated EFS and OS analysis for this trial allow an opportunity to evaluate SMN risk in the context of outcomes. Long-term outcomes were favorable using this risk-adapted approach, with a 10-year EFS and OS of 81.5% and 96.1%, respectively. There was no EFS or OS benefit for patients with an RER and CR

treated with IFRT, which represented 45% of all patients. Current trials using FDG-PET for response assessment are likely able to identify a higher percentage of rapid early responders for which RT may not be required to maintain excellent outcomes. Avoidance of RT without compromising EFS should remain a high priority to reduce risk of SMN. AHOD0031 also evaluated treatment augmentation with DECA for patients with a slow early response. DECA was not associated with an increased risk for SMNs but also did not improve EFS or OS. Novel agents such as brentuximab vedotin and checkpoint inhibitors are currently being studied and may offer improved EFS without increasing the risk for SMNs.

In summary, we report the relatively low 10-year cumulative incidence and spectrum of SMNs among pediatric patients with intermediate-risk HL treated on the largest phase 3 trial in pediatric HL reported to date. In our cohort, the risk of secondary AML is low (10-year cumulative incidence, 0.2%). Longer follow-up will be needed to better define the longer-term risk of solid tumor SMNs. With reduction in the use, dose, and field of RT for HL used in this clinical trial compared with older studies,[28-31] we are hopeful that cumulative incidence of solid tumors will also remain low. An understanding of the risks and benefits of this treatment approach is essential to understanding how to manage HL survivors as well as how best to design future clinical trials for children and adolescents with HL.

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Authorship

Contribution: L.G.-R., Q.P., and D.L.F. designed the research and wrote the paper; and all authors analyzed the data and reviewed the manuscript.

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ORCID profile: S.L.W., 0000-0002-5234-4134.

Correspondence: Lisa Giulino-Roth, 525 E 68th St, Payson 695, New York, NY 10065; e-mail: lgr2002@med.cornell.edu.

Footnotes

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For original data, please e-mail the corresponding author.

The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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