Trends in risk for therapy-related myelodysplastic syndrome/acute myeloid leukemia after initial chemo/immunotherapy for common and rare lymphoid neoplasms, 2000–2018

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Summary

Background Historically, survivors of common lymphoid neoplasms (LNs) had increased risks for therapy-related myelodysplastic syndrome/acute myeloid leukemia (tMDS/AML). Despite major treatment advances in the treatment of LNs over the last two decades, a comprehensive evaluation of tMDS/AML trends following both common and rare LNs treated in this contemporary period is lacking.

Methods In US cancer registries during 2000–2018, we identified 1496 tMDS/AML cases among 186,503 adults who were treated with initial chemo/immunotherapy for first primary LN and survived ≥1 year. We quantified tMDS/AML standardized incidence ratios (SIRs), excess absolute risks (EARs, per 10,000 person-years), and cumulative incidence.

Findings The highest tMDS/AML risks occurred after precursor leukemia/lymphoma (SIR = 39, EAR = 30), Burkitt leukemia/lymphoma (SIR = 20, EAR = 24), peripheral T-cell lymphoma (SIR = 12, EAR = 23), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; SIR = 9.0, EAR = 27), and mantle cell lymphoma (SIR = 8.5, EAR = 25). Elevated risks (SIRs = 4.2–6.9, EARs = 4.9–15) also were observed after all other LN subtypes except hairy cell leukemia and mycosis fungoides/Sézary syndrome. Among patients treated more recently, tMDS/AML risks were significantly higher after CLL/SLL ($SIR_{2000\text{-}2005}$ = 4.8, $SIR_{2012\text{-}2017}$ = 10, P_{trend} = 0.0043), significantly lower after Hodgkin ($SIR_{2000\text{-}2005}$ = 15, $SIR_{2012\text{-}2017}$ = 6.3, P_{trend} = 0.024) and marginal zone ($SIR_{2000\text{-}2005}$ = 7.5, $SIR_{2012\text{-}2017}$ = 2.3, P_{trend} = 0.015) lymphomas, and non-significantly lower after mantle cell lymphoma ($SIR_{2000\text{-}2005}$ = 10, $SIR_{2012\text{-}2017}$ = 3.2, P_{trend} = 0.054), lymphoplasmacytic lymphoma/Waldenström macroglobulinemia ($SIR_{2000\text{-}2005}$ = 6.9, $SIR_{2012\text{-}2017}$ = 1.0, P_{trend} = 0.067), and plasma cell neoplasms ($SIR_{2000\text{-}2005}$ = 5.4, $SIR_{2012\text{-}2017}$ = 3.1, P_{trend} = 0.051). EAR and cumulative incidence trends generally were similar to SIR trends. Median survival after tMDS/AML was 8.0 months (interquartile range, 3.0–22.0).

Interpretation Although tMDS/AML risks are significantly elevated after initial chemo/immunotherapy for most LNs, patients treated more recently have lower tMDS/AML risks, except after CLL/SLL. Though rare, the poor prognosis following tMDS/AML emphasizes the importance of continued efforts to reduce treatment-associated toxicity.

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Keywords: Treatment-related leukemia; Lymphoma; Lymphoid neoplasm; Survivorship

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Research in context

Evidence before this study

The occurrence of therapy-related myelodysplastic syndrome/acute myeloid leukemia (tMDS/AML) is well-established as a rare but frequently fatal adverse outcome for patients treated with chemotherapy for common lymphoid neoplasms (LNs). We searched PubMed for population-based studies and clinical series published in English through December 2022 with key terms "treatment-related leukemia," "therapy-related leukemia," and "therapy-related myeloid neoplasms" in LN patients treated in a contemporary era. There were no comprehensive evaluations of tMDS/AML trends following both common and rare LNs for patients treated in the 2000s.

Added value of this study

This study provides, to our knowledge, the first contemporary comprehensive, population-based assessment of the risks of tMDS/AML among patients treated with initial chemo/immunotherapy for a broad range of LN subtypes, as well as investigating how tMDS/AML risks have changed in the last two decades. The variation in tMDS/AML risks we observed among LN subtypes and the patterns in risks over the study period appeared to coincide with US treatment patterns for many LN subtypes. This study provides insights that are difficult to glean from clinical trials and case series that typically are based on smaller numbers of selected patients and do not reflect the general population experience due to the selected nature of patients and the typically limited duration of follow-up.

Implications of all the available evidence

Population-based data show that patients treated with initial chemo/immunotherapy for a broad array of LNs may face increased tMDS/AML risks, and that these risks have evolved consistent with changes in treatment practices for certain subtypes. Although tMDS/AML is rare, the poor survival emphasizes the high fatality rate and the need to continue to understand and reduce treatment-related toxicity.

Introduction

As early as the 1970s, patients with common lymphoid neoplasm (LN) subtypes were recognized to have high risk of therapy-related myelodysplastic syndrome/acute myeloid leukemia (tMDS/AML).[1–7] Since that time, treatment approaches for lymphoid neoplasms along with supportive measures (e.g., growth factors, antibiotics/antivirals) have evolved substantially, resulting in marked improvements in survival following many lymphoid neoplasm subtypes.[8–11] Particularly in the last two decades, certain patients have been treated using risk-adapted approaches that have enabled de-intensification of therapy, numerous new agents have been introduced (Appendix Table S1),[12,13] and increasing recognition of rare LN subtypes has resulted in greater diagnostic specificity.[14] However, evolving trends in tMDS/AML risks after common lymphoid neoplasms over the recent two decades have not been investigated, and tMDS/AML risks and trends after rare subtypes have not been comprehensively quantified.

We therefore comprehensively investigated tMDS/AML risks after contemporary treatment for both common and rare LN subtypes in a population-based cohort of patients treated with initial chemotherapy and/or immunotherapy (chemo/immunotherapy). We quantified overall and LN subtype-specific risks and temporal trends during 2000–2018, and estimated tMDS/AML relative risk as well as measures of absolute risk to understand the clinical impacts of tMDS/AML occurrence. The study leverages the expansion of the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) population-based cancer registry program in 2000, which also coincided with the requirement to report MDS to SEER and the introduction of the World Health Organization Classification for Hematopoietic and Lymphoid Tissues, allowing for more consistent registry-based classification of LN subtypes.[14]

Methods

Study population and outcomes

We identified a cohort of patients who were diagnosed with a first primary lymphoid malignancy at ages 20–84 years during 2000–2017, survived ≥1 year after diagnosis without developing a second malignancy, and were treated with initial chemo/immunotherapy, as reported to 17 SEER cancer registry areas encompassing 27.8% of the United States population.[9] Individuals aged <20 years were excluded from these analyses because treatment approaches may differ for pediatric patients,[15] and their tMDS/AML risks have been reported recently.[16]

Lymphoid malignancy subtypes were classified according to the World Health Organization Classification using International Classification of Diseases for Oncology, Third Edition (ICD-O-3) morphology codes.[14,17,18] For lymphoid malignancy subtypes that are classified using Ann Arbor stage, patients were grouped as having either stage I/II or III/IV disease at diagnosis. Data for other staging schema (e.g., Rai or Binet staging system for chronic lymphocytic leukemia [CLL], International Staging System [ISS] or revised-ISS for multiple myeloma) were not available. Major categories of initial treatment (chemotherapy, immunotherapy, radiotherapy) were recorded by the cancer registries; detailed data were not available for specific agents, doses, and duration of use; radiation fields and doses; or

subsequent treatment for relapsed/refractory disease. Notably, this analysis was restricted to the evaluation of patients who received initial chemo/immunotherapy combined as a single category because SEER classified certain immunotherapies (e.g., rituximab, alemtuzumab) as chemotherapy through 2012 but then changed their classification to immunotherapy beginning in 2013 (Appendix Table S1).[19] We focused on chemo/immunotherapy because of its major role in tMDS/AML risk and the vast majority of patients received initial chemo/immunotherapy rather than initial radiotherapy (Table 1).

Cases of histologically confirmed second primary MDS or AML were identified using ICD-O-3 morphology codes (9727, 9840, 9861–9931, 9980–9992).[14,20–22] We used the term "tMDS/AML" to describe all second primary MDS or AML occurring among patients previously treated with initial chemo/immunotherapy. Specific tMDS/AML subtypes were not evaluated because of the large proportion of cases coded to "therapy-related MDS/AML" or unspecified. Patients were actively followed by the registries for vital status.

Statistical analysis

For each analysis, patients were considered at risk for tMDS/AML beginning one year after lymphoid malignancy diagnosis until the first of: second primary cancer diagnosis, death, age 85 years, or end of study (December 31, 2018, the most recent available data for the 17 registries included in this analysis). We excluded person-time within the first year to reduce bias resulting from systematically greater medical surveillance during lymphoid malignancy diagnosis and initial treatment compared with the general population, and censored at age 85 years to reduce bias resulting from decreased surveillance among elderly individuals.[23] Descriptive statistics are consistently provided as the median and interquartile range (IQR).

We estimated the relative risk of tMDS/AML occurring after initial chemo/immunotherapy for lymphoid neoplasms compared with that expected in the general population using standardized incidence ratios (SIR = observed/expected), with exact, Poisson-based 95% confidence intervals (CIs). Expected numbers of cases were estimated based on incidence rates for MDS/AML in the total population of the same 17 SEER registries, stratifying by key demographic characteristics, including age (5-year groups), race (white/unknown, black, other), sex, and calendar year (2000–2005, 2006–2011, 2012–2018). For LN types with ≥10 tMDS/AML cases, we analyzed calendar year trends in tMDS/AML risk, restricted to tMDS/AML risks occurring within the first five years following LN diagnosis to allow similar person-time at risk in each calendar year period. Multivariable Poisson regression models tested for calendar year trends in the SIRs using a likelihood ratio statistic, adjusting for sex and age at LN diagnosis and including the log of the expected number of cases as an offset to indirectly adjust for attained age and calendar year.[24]

We also conducted a series of analyses to understand the clinical impacts of tMDS/AML occurrence. First, we estimated tMDS/AML excess absolute risk (EAR = [observed–expected] × 10,000 person-years). We also calculated cumulative incidence of tMDS/AML, accounting for competing risks of incident other hematologic malignancies and solid tumors as well as death due to hematologic malignancy, solid tumors, or non-cancer causes.[25] Finally, we calculated median survival following tMDS/AML diagnosis.

For all analyses, a two-sided $P < 0.05$ was considered statistically significant. SIRs and EARs were calculated using SEER*Stat software, version 8.3.9 (National Cancer Institute, Bethesda, MD), whereas Poisson regression, cumulative incidence, and median survival analyses were conducted using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

Ethics statement

Because this analysis used only de-identified data collected through the SEER Registry Program and obtained through a Data Use Agreement, the study was not considered human subjects research and thus did not require review by an Institutional Review Board.

Role of the funding source

The study sponsor had no role in study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Results

Among a total of 317,721 patients who survived ≥1 year after diagnosis with a first primary LN during the study period, our cohort included the 186,503 (58.7%) individuals who were treated with initial chemo/immunotherapy, as reported to the cancer registries (Table 1). This fraction represented the majority (67%–95%) of patients with first primary Hodgkin lymphoma, precursor leukemia/lymphoma, Burkitt leukemia/lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma (DLBCL), hairy cell leukemia, and plasma cell neoplasms; about half the patients with lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, follicular lymphoma, and peripheral T-cell lymphoma (PTCL); and a minority (<35%) of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), marginal zone lymphoma, and mycosis fungoides/Sézary syndrome. Among those treated with initial chemo/immunotherapy, median age at diagnosis ranged from 53.5 to 67.5 years, except for Hodgkin lymphoma (37.5, IQR = 27.5–51.5 years), precursor leukemia/lymphoma (40.5, IQR = 28.5–54.5

Lymphoid neoplasm type	Total[a]	Received initial chemo/immunotherapy							Median person-years at risk (IQR, years)
		Total	Median age at diagnosis (IQR, years)	Male	Initial radio-therapy	Ann Arbor stage			
						I/II	III/IV	Unknown/NA	
	N	N (%)[b]		N (%)	N (%)	N (%)	N (%)	N (%)	
Total	317,721	186,503 (58.7)	60.5 (48.5–69.5)	105,261 (56.4)	38,149 (20.5)	55,016 (29.5)	68,457 (36.7)	63,030 (33.8)	3.9 (1.5–8.1)
Hodgkin lymphoma	28,321	23,991 (84.7)	37.5 (27.5–51.5)	13,013 (54.2)	8230 (34.3)	13,724 (57.2)	9597 (40.0)	670 (2.8)	6.6 (2.8–11.3)
Precursor leukemia/lymphoma	6131	5852 (95.4)	40.5 (28.5–54.5)	3425 (58.5)	1534 (26.2)		NA		2.1 (0.7–5.7)
Burkitt leukemia/lymphoma	2284	2180 (95.4)	45.5 (34.5–57.5)	1577 (72.3)	197 (9.0)	799 (36.7)	1169 (53.6)	212 (9.7)	5.3 (2.0–9.7)
CLL/SLL	58,160	11,856 (20.4)	64.5 (56.5–73.5)	7685 (64.8)	266 (2.2)		NA		4.0 (1.7–7.4)
Mantle cell lymphoma	6851	5363 (78.3)	64.5 (56.5–71.5)	3885 (72.4)	442 (8.2)	682 (12.7)	4455 (83.1)	226 (4.2)	3.2 (1.3–6.3)
LPL/WM	6136	3148 (51.3)	67.5 (58.5–75.5)	1912 (60.7)	53 (1.7)		NA		3.8 (1.5–7.2)
DLBCL	55,813	48,644 (87.2)	61.5 (49.5–71.5)	26,990 (55.5)	12,565 (25.8)	23,953 (49.2)	23,081 (47.4)	1610 (3.3)	4.1 (1.5–8.4)
Marginal zone lymphoma	19,305	6503 (33.7)	63.5 (54.5–72.5)	2987 (45.9)	760 (11.7)	2341 (36.0)	3609 (55.5)	553 (8.5)	4.4 (1.8–8.0)
Follicular lymphoma	38,914	22,138 (56.9)	60.5 (51.5–69.5)	11,324 (51.2)	2652 (12.0)	7027 (31.7)	14,216 (64.2)	895 (4.0)	5.4 (2.3–9.7)
Hairy cell leukemia	3438	2449 (71.2)	53.5 (46.5–62.5)	1986 (81.1)	4 (0.2)		NA		6.8 (3.3–11.3)
MF/SS	5881	1250 (21.3)	57.5 (47.5–67.5)	764 (61.1)	185 (14.8)		NA		4.4 (1.5–8.7)
PTCL	8780	4696 (53.5)	57.5 (45.5–67.5)	2834 (60.3)	871 (18.5)	1759 (37.5)	2703 (57.6)	234 (5.0)	3.2 (1.0–7.5)
Plasma cell neoplasms	56,259	37,720 (67.0)	64.5 (56.5–71.5)	21,030 (55.8)	8620 (22.9)		NA		2.6 (1.1–5.2)

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; IQR, interquartile range; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; MF/SS, mycosis fungoides/Sezary syndrome; NA, not applicable; PTCL, peripheral T-cell lymphoma; SD, standard deviation. [a]Patients were diagnosed with a first primary lymphoid neoplasm at ages 20–84 years and survived ≥1 year without developing a second malignancy, as reported in 17 population-based cancer registries of the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program, 2000–2017, with follow-up through 2018. Registries included Connecticut; Detroit; Atlanta, greater Georgia, and rural Georgia; Los Angeles, San Francisco–Oakland, San Jose–Monterey, and greater California; Hawaii; Iowa; Kentucky; Louisiana; New Mexico; New Jersey; Seattle-Puget Sound; and Utah. [b]Percentage of patients who received initial chemo/immunotherapy among the total patients diagnosed. All other percentages are among patients who received initial chemo/immunotherapy.

Table 1: **Patient and clinical characteristics of the study cohort.**

years), and Burkitt leukemia/lymphoma (45.5, IQR = 34.5–57.5 years). Most lymphoid neoplasms initially treated with chemo/immunotherapy exhibited a male predominance (>50%) except marginal zone lymphoma (N = 2987/6503, 45.9% male). Initial therapy also included radiotherapy for a minority of patients, most commonly for Hodgkin lymphoma (N = 8230/23,991, 34.3%), precursor leukemia/lymphoma (N = 1534/5852, 26.2%), DLBCL (N = 12,565/48,644, 25.8%), and plasma cell neoplasms (N = 8620/37,720, 22.9%).

A total of 1496 tMDS/AML cases were diagnosed during a median follow-up of 3.9 (IQR = 1.5–8.1) years, an incidence rate 6.4 times (95%CI 6.1–6.7) that expected in the general population, corresponding to an EAR of 12.8 cases per 10,000 person-years (Table 2). The most strikingly elevated tMDS/AML SIRs and EARs were observed after initial chemo/immunotherapy for precursor leukemia/lymphoma (SIR = 39, EAR = 30), Burkitt leukemia/lymphoma (SIR = 20, EAR = 24), peripheral T-cell lymphoma (SIR = 12, EAR = 23), CLL/SLL (SIR = 9.0, EAR = 27), and mantle cell lymphoma (SIR = 8.5, EAR = 25). Significantly elevated risks (SIRs = 4.2–6.9, EARs = 4.9–15) also were observed after initial chemo/immunotherapy for Hodgkin lymphoma, follicular lymphoma, plasma cell neoplasms, DLBCL, LPL/WM, and marginal zone lymphoma. In contrast, tMDS/AML risk was not significantly elevated after initial chemo/immunotherapy for hairy cell leukemia and mycosis fungoides/Sézary syndrome. Similarly, analyses of the 10-year cumulative incidence of tMDS/AML showed the highest risks (>1.0%) among patients treated with initial chemo/immunotherapy for Burkitt leukemia/lymphoma (2.0%), CLL/SLL (1.9%), mantle cell lymphoma (1.7%), precursor leukemia/lymphoma (1.4%), PTCL (1.4%), follicular lymphoma (1.3%), and LPL/WM (1.1%), after accounting for competing risks of other second malignancies and death (Appendix Figure S1, Table S2). Although the tMDS/AML incidence was generally lower than that of other competing causes, median survival after tMDS/AML was only 8.0 (IQR = 3.0–22.0) months.

In analyses by latency (Table 3), tMDS/AML SIRs and EARs generally were higher 1–4.9 years compared with ≥5 years after diagnosis of most LN subtypes initially treated with chemo/immunotherapy, with significant differences by latency period in the SIRs observed for Hodgkin lymphoma, precursor leukemia/lymphoma, Burkitt leukemia/lymphoma, DLBCL, follicular lymphoma, and peripheral T-cell lymphoma. Notably, however, SIRs remained statistically significantly elevated ≥5 years after diagnosis for nearly all LN subtypes.

To evaluate the potential impacts of evolving initial chemo/immunotherapy treatment approaches, we compared tMDS/AML risks within five years of LN diagnosis during 2000–2005, 2006–2011, and 2012–2017. In analyses of SIRs (Fig. 1, Appendix Table S3), tMDS/AML risks after initial chemo/immunotherapy for CLL/SLL were significantly higher for patients treated more recently compared to those treated earlier in the study period ($SIR_{2000\text{-}2005}$ = 4.8, $SIR_{2006\text{-}2011}$ = 13, $SIR_{2012\text{-}2017}$ = 10; P_{trend} = 0.0043). In contrast, tMDS/AML risks declined significantly among patients treated more recently for Hodgkin lymphoma ($SIR_{2000\text{-}2005}$ = 15, $SIR_{2006\text{-}2011}$ = 7.1, $SIR_{2012\text{-}2017}$ = 6.3; P_{trend} = 0.024) and marginal zone lymphoma ($SIR_{2000\text{-}2005}$ = 7.5, $SIR_{2006\text{-}2011}$ = 4.6, $SIR_{2012\text{-}2017}$ = 2.3; P_{trend} = 0.015).

Lymphoid neoplasm type	N	SIR	(95%CI)	EAR per 10,000 person-years	5-year cumulative incidence	(95%CI)	10-year cumulative incidence	(95%CI)
Total	1496	6.4	(6.1, 6.7)	13	0.57%	(0.53%, 0.61%)	1.0%	(1.0%, 1.1%)
Hodgkin lymphoma	101	6.9	(5.6, 8.4)	4.9	0.28%	(0.20%, 0.35%)	0.48%	(0.38%, 0.58%)
Precursor leukemia/lymphoma	69	39	(30, 49)	30	1.3%	(0.95%, 1.6%)	1.4%	(1.1%, 1.8%)
Burkitt leukemia/lymphoma	34	20	(14, 27)	24	1.1%	(0.65%, 1.6%)	2.0%	(1.3%, 2.7%)
CLL/SLL	184	9.0	(7.8, 10)	27	1.0%	(0.82%, 1.2%)	1.9%	(1.6%, 2.2%)
Mantle cell lymphoma	66	8.5	(6.6, 11)	25	0.85%	(0.58%, 1.1%)	1.7%	(1.3%, 2.2%)
LPL/WM	29	4.9	(3.3, 7.0)	15	0.64%	(0.33%, 1.0%)	1.1%	(0.64%, 1.6%)
DLBCL	365	5.3	(4.7, 5.8)	11	0.56%	(0.49%, 0.63%)	1.0%	(0.88%, 1.1%)
Marginal zone lymphoma	44	4.2	(3.1, 5.7)	9.5	0.46%	(0.28%, 0.64%)	0.94%	(0.65%, 1.2%)
Follicular lymphoma	241	6.7	(5.9, 7.6)	15	0.65%	(0.53%, 0.76%)	1.3%	(1.1%, 1.5%)
Hairy cell leukemia	6	1.5	(0.5, 3.3)	1.1	0.04%	(0.00%, 0.12%)	0.17%	(0.00%, 0.37%)
MF/SS	<3	1.3	(0.2, 4.7)	0.7	0.09%	(0.00%, 0.27%)	0.09%	(0.00%, 0.27%)
PTCL	55	12	(9.1, 16)	23	0.95%	(0.65%, 1.2%)	1.4%	(1.0%, 1.8%)
Plasma cell neoplasms	213	5.4	(4.7, 6.2)	13	0.42%	(0.35%, 0.49%)	0.80%	(0.69%, 0.92%)

Abbreviations: CI, confidence interval; EAR, excess absolute risk; SIR, standardized incidence ratio; tMDS/AML, therapy-related myelodysplastic syndrome/acute myeloid leukemia. NOTE: Exact counts were suppressed when <3 cases were observed to protect patient confidentiality.

Table 2: **Relative risk, excess absolute risk, and 5- and 10-year cumulative incidence of tMDS/AML after initial chemo/immunotherapy for a first primary lymphoid neoplasm, 2000–2018.**

	1–4.9 years				≥5 years				SIR
	N	SIR	(95%CI)	EAR[a]	N	SIR	(95%CI)	EAR[a]	$P_{difference}$[b]
Total	886	7.1	(6.7, 7.6)	14	610	5.6	(5.2, 6.0)	11	<0.0001
Hodgkin lymphoma	57	9.2	(6.9, 11.9)	6.5	44	5.2	(3.8, 7.0)	3.7	<0.0001
Precursor leukemia/lymphoma	61	64.4	(49.2, 82.7)	47	8	9.5	(4.1, 18.8)	7.2	<0.0001
Burkitt leukemia/lymphoma	20	25.3	(15.4, 39.1)	29	14	14.8	(8.1, 24.8)	19	0.022
CLL/SLL	106	9.3	(7.7, 11.3)	27	78	8.6	(6.8, 10.7)	27	0.096
Mantle cell lymphoma	37	8.1	(5.7, 11.1)	23	29	9.1	(6.1, 13.0)	29	0.061
LPL/WM	15	4.4	(2.5, 7.3)	13	14	5.5	(3.0, 9.2)	18	0.48
DLBCL	225	6.3	(5.5, 7.2)	14	140	4.1	(3.5, 4.9)	8.5	<0.0001
Marginal zone lymphoma	26	4.7	(3.1, 6.9)	11	18	3.7	(2.2, 5.8)	8.3	0.099
Follicular lymphoma	119	7.2	(6.0, 8.7)	15	122	6.2	(5.2, 7.4)	15	0.00054
Hairy cell leukemia	<3	0.7	(0.0, 3.7)	−0.6	5	2.0	(0.7, 4.7)	2.5	[b]
MF/SS	<3	1.3	(0.0, 7.5)	0.7	<3	1.3	(0.0, 7.1)	0.6	[b]
PTCL	38	15.8	(11.2, 21.6)	30	17	7.9	(4.6, 12.6)	14	0.0082
Plasma cell neoplasms	126	4.8	(4.0, 5.7)	11	87	6.7	(5.4, 8.3)	17	0.66

NOTE: Exact counts were suppressed when <3 cases were observed to protect patient confidentiality. [a]EAR per 10,000 person-years. [b]$P_{difference}$ derived from multivariable adjusted Poisson regression models adjusted for sex, year of lymphoid neoplasm diagnosis (2000–2004, 2005–2009, and 2010–2017), and age at lymphoid neoplasm diagnosis (20–34,35-44, 45–59, 60–74, 75–84 years). The log of the expected number of cases was included as an offset to indirectly adjust for attained age and calendar year. Models were not constructed when one comparison group had <3 observed cases.

Table 3: **Relative risk and excess absolute risk for tMDS/AML after initial chemo/immunotherapy for a first primary lymphoid neoplasm, 2000–2018, by time since lymphoid neoplasm diagnosis.**

Additionally, we observed a borderline significant decline in tMDS/AML risks over the study period, with lower SIRs particularly in the most recent calendar period, following mantle cell lymphoma (P_{trend} = 0.054), lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (P_{trend} = 0.067), and plasma cell neoplasms (P_{trend} = 0.051). Notably, there was no temporal change in tMDS/AML risk after initial chemo/immunotherapy for DLBCL (P_{trend} = 0.25).

The calendar year trends observed for the SIRs generally were comparable in analyses of cumulative incidence and EARs (Appendix Tables S3 and S4). For patients treated with initial chemo/immunotherapy for

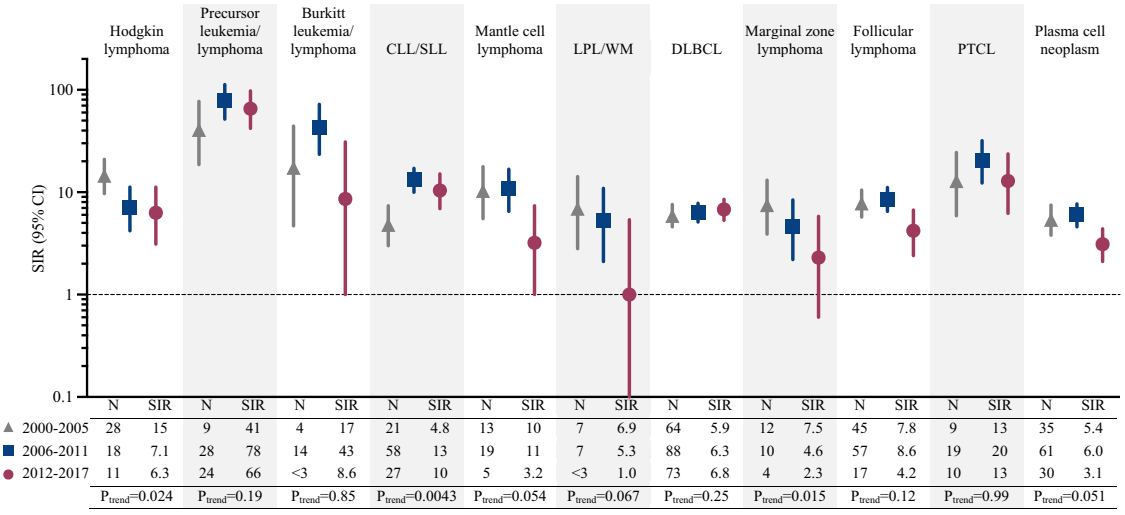

Fig. 1: Relative risk for tMDS/AML occurring within 5 years after initial chemo/immunotherapy for a first primary lymphoid neoplasm, 2000–2018, by calendar year of diagnosis. Note: Confidence intervals for the SIRs are provided in Appendix Table S3. Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; PTCL, peripheral T-cell lymphoma; SIR, standardized incidence ratio; tMDS/AML, therapy-related myelodysplastic syndrome/acute myeloid leukemia.

CLL/SLL, the only subtype with significantly increasing SIRs over calendar time during the study period, the 5-year cumulative incidence of tMDS/AML increased from 0.49% for patients treated during 2000–2005 to 1.5% and 1.1% for patients treated during 2006–2011 and 2012–2017, respectively. Reassuringly, the subtypes with significantly decreasing SIRs during the study period also demonstrated decreasing 5-year cumulative incidence (Hodgkin lymphoma: 2000–2005 = 0.38%, 2006–2011 = 0.22%, 2012–2017 = 0.20%; marginal zone lymphoma: 2000–2005 = 0.71%, 2006–2011 = 0.47%, 2012–2017 = 0.19%).

Discussion

This study provides, to our knowledge, the first contemporary comprehensive, population-based assessment of the risks of tMDS/AML among patients treated with initial chemo/immunotherapy for a broad range of LN subtypes, as well as investigating how tMDS/AML risks have changed in the last two decades. Using large-scale population-based cancer registry data with systematic long-term follow-up, we demonstrate that patients treated with initial chemo/immunotherapy for numerous lymphoid neoplasms during the last two decades face increased risk of developing tMDS/AML, although the risks vary by both disease subtype and calendar year period. Notably, this report is the first, to our knowledge, to provide quantitative, population-based estimates of tMDS/AML risks after less common LN subtypes and to investigate how tMDS/AML risks have changed during 2000–2018. The highest risks were observed after initial chemo/immunotherapy for precursor leukemia/lymphoma, Burkitt leukemia/lymphoma, peripheral T-cell lymphoma, CLL/SLL, and mantle cell lymphoma. tMDS/AML risks following initial chemo/immunotherapy for CLL/SLL were higher for patients treated more recently compared with those treated in the early 2000s. However, for most other subtypes, the risks have declined for patients treated more recently, providing support for ongoing clinical efforts to reduce toxicity as treatment approaches for lymphoid neoplasms continue to evolve.

Among all the patients we evaluated, only those who received initial chemo/immunotherapy for CLL/SLL had higher tMDS/AML risks for patients treated since the mid 2000s compared with the early 2000s. This change in tMDS/AML risk is coincident with the increased use of fludarabine, a known leukemogen, and possibly the use of the alkylating agent bendamustine as substitutes for chlorambucil or cyclophosphamide-based regimens.[26–28] The slightly lower risk for patients with CLL/SLL treated in 2012–2017 compared with 2006–2011 warrants further follow-up of more recently treated patients in population-based cancer registries as treatment approaches for CLL/SLL continue to evolve (e.g., Bruton tyrosine kinase inhibitors, B-cell lymphoma 2 (BCL-2) inhibitors, and others), particularly because tMDS/AML cases would not be identified in many clinical trials that are of inadequate size to identify this rare treatment-related outcome.

Among other common LN subtypes, we observed lower tMDS/AML risks after both Hodgkin lymphoma and plasma cell neoplasms compared with previous reports that included patients treated historically (pre-2000).[2,5,29,30] Our multivariable model results suggested that these declines in tMDS/AML risk have continued even during 2000–2018. These findings likely reflect the decreased frequency and duration of use of known highly leukemogenic agents, specifically, melphalan for plasma cell neoplasms and nitrogen mustard for Hodgkin lymphoma, and also the utilization of risk-adapted treatment approaches.[5,31–33] Nevertheless, the persistent risks and reported leukemogenicity of lenalidomide support continued evaluation of tMDS/AML risks after plasma cell neoplasms.[34] For patients with follicular lymphoma, the non-significantly lower risks of tMDS/AML we observed for patients treated in the most recent period (2012–2017) warrants further monitoring, particularly with the introduction of bendamustine and more recently, chimeric antigen receptor (CAR) T-cell therapy.[35–37] The consistency over time of tMDS/AML risk after DLBCL likely reflects the long-term and ongoing use of the R-CHOP regimen over the last two decades.[38]

Some of the highest tMDS/AML risks we observed occurred following Burkitt leukemia/lymphoma, likely reflecting the intensive treatment regimens with multiple known leukemogenic agents (e.g., etoposide, cyclophosphamide, doxorubicin) required for this aggressive lymphoid neoplasm.[39] We also observed strikingly elevated tMDS/AML risks after intensive chemo/immunotherapy for precursor leukemia/lymphoma,[40] consistent with previous reports in children.[16] The higher absolute risk of tMDS/AML following these subtypes emphasizes the importance of assessing risks and benefits of treatment approaches, particularly for Burkitt lymphoma, which has a substantially better prognosis than precursor leukemia/lymphoma in adults.[8–10]

tMDS/AML risks also were significantly elevated following initial chemo/immunotherapy for other less common lymphoid neoplasms, including 8- to 12-fold increased risks after peripheral T-cell lymphoma and mantle cell lymphoma, and 4- to 5-fold increased risks after marginal zone lymphoma and LPL/WM. The tMDS/AML risks following peripheral T-cell and mantle cell lymphomas are consistent with the known leukemogenicity of the intensive anthracycline- and cyclophosphamide-based regimens that are typically used to treat these aggressive subtypes.[41] In contrast, tMDS/AML risks were lower after the more indolent LPL/WM and marginal zone lymphomas where anti-CD20-based monotherapy is included among the

effective treatment options.[42,43] Similar to follicular lymphoma, the suggestively decreased tMDS/AML SIRs for patients treated in the most recent period (2012–2017) for mantle cell lymphoma, LPL/WM, and marginal zone lymphoma warrant additional follow-up of more recently treated patients.

Unlike nearly all other LN subtypes, we did not observe elevated risk for tMDS/AML after initial chemo/immunotherapy for either hairy cell leukemia or mycosis fungoides/Sézary syndrome. These results are consistent with the treatment of these LN subtypes with agents that are not typically considered leukemogenic, including cladribine for hairy cell leukemia and immunomodulatory agents for mycosis fungoides/Sézary syndrome.[44–46] Notably, the individuals in our study with initial chemo/immunotherapy for mycosis fungoides/Sézary syndrome likely reflects the small fraction of patients who received systemic therapy, as SEER does not capture use of topical therapies.

The large-scale and population-based nature of these data, systematic long-term follow-up, and inclusion of both common and rare lymphoid neoplasms enable this study to provide valuable insights into tMDS/AML risks that complement results from clinical trials and case series that typically are based on smaller numbers of selected patients and thus do not reflect the general population experience. Although the leukemogenicity of many newer agents is not yet well understood, it is notable that some (e.g., bendamustine, lenalidomide) are labeled for second malignancy, emphasizing the importance of monitoring tMDS/AML risks as treatment approaches for lymphoid neoplasms continue to evolve. The SEER program is known to under-ascertain chemotherapy. Additional limitations of the study include the restriction to patients who required initial therapy at the time of diagnosis; lack of detailed data on specific agents and doses; and absence of data on treatment for relapsed/refractory disease, maintenance therapy, or use of hematopoietic stem cell transplantation. These limitations emphasize the importance of specific studies with detailed treatment data to estimate the association and dose–response between specific chemotherapeutic and immunotherapeutic agents and leukemia risk, and factors that could potentially modify risks, such as patient age.[6]

In summary, US population-based cancer registry data demonstrate that patients treated with initial chemo/immunotherapy for most lymphoid neoplasms may face increased tMDS/AML risks, but that tMDS/AML risks have evolved consistent with changes in treatment practices for certain subtypes. Despite the rarity of tMDS/AML, the 8-month median survival after tMDS/AML diagnosis emphasizes the high fatality rate of this rare outcome. Ongoing research to identify patients at the highest risk of tMDS/AML based on patient-specific (e.g., age, exposures), heritable (e.g., germline variation), and acquired (e.g., clonal hematopoiesis, chronic inflammation) factors may allow for risk stratification and early interventions in the future.[47,48] With further advances in therapeutic approaches for lymphoid neoplasms, future studies with additional follow-up, newer therapies, and detailed clinical data will be important for assessing tMDS/AML risks and informing evolving risk/benefit assessments for specific treatment regimens.

Contributors

LMM, GMD, REC, and MSL designed the study and analysis. All authors had access to the data, and LMM, GMD, REC, and CBS verified the data. LMM drafted the original manuscript. LMM, REC, MSL, SJS, PGA, NHD, ECS, and GMD revised the manuscript for intellectual content and made the decision to submit for publication.

Data sharing statement

The data used for this study are available upon application to the SEER Program (seer.cancer.gov).

Declaration of interests

The authors have no relationships to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102060.

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