Published in final edited form as:

Int J Dermatol. 2017 November ; 56(11): 1125–1129. doi:10.1111/ijd.13653.

Risk of Cutaneous T-Cell Lymphoma in Patients With Chronic Lymphocytic Leukemia and Other Subtypes of Non-Hodgkin Lymphoma

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Abstract

Background—Second hematologic cancers in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) are well documented and include Hodgkin lymphoma, therapy-related acute myeloid leukemia/myelodysplastic syndromes, and transformation to diffuse large B-cell lymphoma. Although cutaneous T-cell lymphoma (CTCL) has been reported in patients with CLL, the incidence and comparison to expected rates are unknown. We evaluated the incidence of CTCL among patients with CLL or other non-Hodgkin lymphoma (NHL) subtypes using data from the Surveillance, Epidemiology, and End Results (SEER) Program.

Methods—We searched the SEER 13 registries for patients with a diagnosis of CLL and NHL between 1992 and 2008. Among patients identified, we evaluated the incidence of CTCL.

Results—Among 31,286 patients with CLL, the incidence of CTCL was nonsignificantly higher in men than women: 104.2 (95% CI, 50.0–191.8) and 28.1 (95% CI, 3.4–101.3) per 1,000,000 person-years, respectively ($P=.06$). Among 97,691 patients with NHL, the incidence of CTCL was similar in men and women (97.9 [95% CI, 62.0–146.9] and 92.0 [95% CI, 56.2–142.1] per 1,000,000 person-years, respectively; $P=.84$). The incidence of CTCL among males with CLL (standardized incidence ratio [SIR], 3.0 [95% CI, 1.4–5.5]), males with NHL (SIR, 3.7 [95% CI, 2.3–5.5]), and females with NHL (SIR, 5.9 [95% CI, 3.6–9.1]) was significantly higher than expected in the general population (all $P<.001$).

Conclusion—The risk of CTCL is greater in men with CLL than in the general population. In patients with NHL, both men and women are at greater risk for CTCL than in the general population.

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Conflict of interest: None.

Keywords

CTCL; cutaneous oncology; cutaneous T-cell lymphoma

Introduction

Chronic lymphocytic leukemia (CLL) is among the most common types of cancer. The incidence of CLL is increasing at a rate of 2% to 4% annually since 1992, after tripling from 1958 to 1992 (1). CLL is included in the non-Hodgkin lymphoma (NHL) family and is classified as a low-grade lymphoproliferative malignancy with clonal expansion of B cells (2). Patients with CLL have been shown to be at increased risk for secondary cancers (3–9). Cutaneous neoplasms, such as squamous cell carcinoma, basal cell carcinoma, malignant melanoma, and other rare cutaneous cancers occur more frequently and aggressively in patients with CLL, possibly due to an altered immune system (7,10–14).

Cutaneous lymphomas embody a heterogeneous group of T- and B-cell lymphomas and represent 3.9% of all NHLs (15). In the United States, the incidence of cutaneous T-cell lymphoma (CTCL) has increased since 1973 from 6.4 to 9.6 cases per million people (16). CTCLs include the more common mycosis fungoides and Sézary syndrome (17), as well as other rare T-cell lymphomas such as CD30-positive lymphoproliferative disorders, subcutaneous panniculitis-like T-cell lymphoma, and peripheral T-cell lymphoma. Mycosis fungoides is a generally more indolent form of CTCL, characterized as an epidermotropic proliferation of T lymphocytes, and makes up the majority of cutaneous lymphomas. Sézary syndrome is an aggressive and leukemic form of CTCL defined by the triad of erythroderma, generalized lymphadenopathy, and neoplastic T cells in the skin, lymph nodes, and peripheral blood (18,19).

An association between CTCL and CLL has been described in prior reports (20–33). However, the incidence of CTCL occurring in patients with CLL has not been investigated in a large population-based study. Because the incidence of lymphoma is increasing, along with the population of elderly patients (1), we sought to further elucidate the risk and incidence of CTCL in patients with CLL as well as other non-CLL subtypes of NHL by using the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute.

Materials and Methods

The cohort of interest included patients with CLL/small lymphocytic lymphoma, hereafter referred to as *CLL*, and patients with non-CLL subtypes of NHL, hereafter referred to as *NHL*, that was first diagnosed between 1992 and 2008. Patients were identified from the SEER 13 program registries by using SEER*Stat version 8.1.2 software (34), which provided deidentified, individual-level data. All data were exported and analyzed with SAS version 9.2 software (SAS Institute Inc). Patients with *International Classification of Diseases for Oncology*, 3rd Edition (ICD-O-3) codes 9823 and 9670 were classified as having CLL. Patients with ICD-O-3 codes 9590, 9591, 9596, 9671, 9673, 9675, 9679, 9680, 9684, 9687, 9689, 9690, 9691, 9695, 9698, 9699, 9714, 9719, 9727, and 9729 were

classified as having NHL. In addition, patients with ICD-O-3 codes 9700, 9701, 9702, 9705, 9708, 9709, and 9718 involving a nonskin primary site were also classified as having NHL. The timing of first primary diagnosis of CLL or NHL per patient was defined as the index date. Patients were excluded if the index date was before 1992, if the diagnosis was not histologically confirmed, or if the patient did not have any follow-up after their index date.

Vital status of all patients was monitored through December 2010. Among the cohort of patients described above, patients were also identified as having subsequent CTCL if they had 1 of the following ICD-O-3 diagnoses, histologically confirmed, with a primary site of skin (codes 440–449), consistent with the study by Criscione and Weinstock (35): mycosis fungoides (code 9700), Sézary syndrome (code 9701), mature T-cell lymphoma not otherwise specified (NOS) (code 9702), angioimmunoblastic T-cell lymphoma (code 9705) (although some experts do not believe that angioimmunoblastic T-cell lymphoma is a form of CTCL but that it occurs in the skin secondarily), subcutaneous panniculitis-like T-cell lymphoma (code 9708), cutaneous T-cell lymphoma NOS (code 9709), or primary cutaneous CD30+ T-cell lymphoma (code 9718).

Statistical Analysis

Patients with CLL and NHL were analyzed separately. Within each analysis, patients were excluded if their CTCL diagnosis came before or up to 1 month after that of CLL or NHL. Follow-up duration was calculated from the date of CLL or NHL diagnosis until CTCL diagnosis, last follow-up, or death, whichever occurred first. Sex- and age group-specific incidence density estimates were derived for each analysis using the number of patients with the incident diagnosis (observed) relative to total person-years of observation. Rates were expressed as incidence per 1,000,000 person-years (36), and related exact 95% CIs were derived by assuming that the observed number of cases followed a Poisson distribution and the number of person-years was fixed. Standardized incidence ratios (SIRs) were constructed through comparison of the observed number of CTCL cases with the number expected in the general US population. The expected estimates of CTCL were obtained using the entire population from the SEER 13 registries for 1992 through 2008 and applying the same CTCL criteria outlined in the previous section and stratifying by sex, age (10-year intervals), and spans of calendar years (1992–1995, 1996–1999, 2000–2003, and 2004–2008). Exact 95% CIs for the SIRs were derived by assuming that the number of cases followed a Poisson distribution and the expected number was fixed.

Results

During 1992 through 2008, 133,631 patients of all ages from the SEER 13 program registries were identified with their first diagnosis of histologically confirmed CLL or NHL. Of these patients, 4,545 were excluded for lack of follow-up after the CLL or NHL diagnosis, and 109 were excluded because of a histologically confirmed CTCL diagnosis before or within 1 month after their CLL or NHL diagnosis (69 mycosis fungoides, 2 Sézary syndrome, 1 mature T-cell lymphoma NOS, 1 subcutaneous panniculitis-like T-cell lymphoma, 32 cutaneous T-cell lymphoma NOS, and 4 primary cutaneous CD30+ T-cell

lymphoma). The remaining cohort at risk for subsequent CTCL (N=128,977) comprised 31,286 patients with CLL (24.3%) and 97,691 patients with NHL (75.7%) (Table 1).

Among those with CLL, CTCL developed in 12 patients over a median follow-up of 4.3 (interquartile range, 2.1–7.7) years. The 12 diagnoses were mycosis fungoides in 7 patients, mature T-cell lymphoma NOS in 1, cutaneous T-cell lymphoma NOS in 3, and primary cutaneous CD30+ T-cell lymphoma in 1. Among those with NHL, CTCL developed in 43 patients over a median follow-up of 3.2 (interquartile range, 1.0–7.2) years. These 43 diagnoses were mycosis fungoides in 22 patients, mature T-cell lymphoma NOS in 2, cutaneous T-cell lymphoma NOS in 14, and primary cutaneous CD30+ T-cell lymphoma in 5.

Table 2 summarizes the incidence of CTCL among patients with CLL or NHL, along with the SIRs. Among patients with CLL, the incidence of CTCL per 1,000,000 person-years was higher in men (104.2; 95% CI, 50.0–191.8) than women (28.1; 95% CI, 3.4–101.3), although the difference did not reach statistical significance ($P=.06$). Among males with CLL, the risk of CTCL was significantly higher than expected in the general population (SIR, 3.0; 95% CI, 1.4–5.5; $P<.001$). Among females with CLL, the observed risk of CTCL was not higher than expected (SIR, 1.5; 95% CI, 0.2–5.5; $P=.74$). Among patients with NHL, the incidence of CTCL per 1,000,000 person-years was similar in men (97.9; 95% CI, 62.0–146.9) and women (92.0; 95% CI, 56.2–142.1; $P=.84$). The risk of CTCL among males with NHL (SIR, 3.7; 95% CI, 2.3–5.5) and among females with NHL (SIR, 5.9; 95% CI, 3.6–9.1) was significantly higher than expected in the general population (both $P<.001$).

Discussion

To our knowledge, this is the first large population-based study investigating the incidence of CTCL in patients with CLL and NHL. We found that the risk of CTCL in men with CLL is significantly greater than in the general population. However, the risk of CTCL was not increased in women with CLL. In both men and women with NHL, the risk of CTCL was greater than in the general population.

Although the proliferation of 2 separate lymphocytic lineages is rare, this study shows that patients with CLL or NHL are at increased risk for CTCL development. Several hypotheses have been presented to explain this phenomenon, such as that these cells 1) come from a common stem cell progenitor or genetic events; 2) occur secondary to carcinogens, viruses, cytokines from T-cell or B-cell clones, or treatment of the preexisting lymphoproliferative disease; or 3) occur by coincidence (33). CLL/NHL is also associated with an altered immune system, which can potentially contribute to the development of secondary malignancy (7). The development of CTCL in patients with CLL appears to be multifaceted.

This study aligns with reports that have described CTCL occurring in patients with CLL (20–33). Among these reports, the largest series consisted of 14 patients, of which 8 had concurrent diagnoses of CLL and CTCL, 5 patients had CLL diagnosed first, and 1 patient had CTCL diagnosed first (33). In that study, the authors noted that patients with CLL and concurrent CTCL appeared to have worse overall median survival (12 months) than patients

with a prior history of CLL and later diagnosis of CTCL (47 months) (33). Although the mechanism is unclear, the behavior of CTCL in patients with CLL may be more aggressive because of the immunosuppression associated with CLL. Management of CTCL may need to be adjusted in the setting of CLL to account for this consideration.

Of interest, in the current study, the female patients with CLL did not have an increased risk of CTCL. In contrast, the incidence of CTCL in women with NHL who were younger than 50 years was quite high; Table 3 shows the sites and dates of development of CTCL among these 5 women. The reason for the different incidence of CTCL in women of different ages is unknown. Further research will be needed to elucidate these differences.

Limitations of this study include those inherent to registry database studies, such as selection bias, coding of events not being primarily for research purposes, and potential inputting errors in the data (37). The strengths of the SEER database itself include the wealth of data that can be used to categorize cancers and the ability to perform epidemiologic analyses on cancers with a large and comprehensive database (38).

In conclusion, CLL/NHL is among the most common types of cancer, and the incidence is increasing. Patients with CLL/NHL are in an immunocompromised state. Although patients with CLL/NHL are more commonly known to be at higher risk for cutaneous neoplasms such as squamous cell carcinoma, basal cell carcinoma, and melanoma, CLL/NHL is less commonly known to be associated with CTCL. This study confirms that those with CLL/NHL are at higher risk for CTCL. Providers should be aware of this association because CTCL can be a source of morbidity in this immunocompromised population. Increased awareness of this association by physicians and other health care providers could afford earlier recognition and more prompt management of CTCL in patients with CLL/NHL.

Abbreviations

CLL	chronic lymphocytic leukemia
CTCL	cutaneous T-cell lymphoma
ICD-O-3	<i>International Classification of Diseases for Oncology</i> , 3rd Edition
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
SEER	Surveillance, Epidemiology, and End Results
SIR	standardized incidence ratio

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Table 1

Characteristics of 128,977 Patients With CLL or NHL in the SEER 13 Program Registries, 1992–2008

Characteristic	Group ^a	
	CLL ^b (n=31,286)	NHL ^c (n=97,691)
Sex		
Male	18,376 (58.7)	52,975 (54.2)
Female	12,910 (41.3)	44,716 (45.8)
Race		
White	27,760 (88.7)	82,535 (84.5)
Black	2,089 (6.7)	6,545 (6.7)
Other	932 (3.0)	7,919 (8.1)
Unknown	505 (1.6)	692 (0.7)
Age at first CLL or NHL diagnosis, y	69.3 (12.5)	62.6 (17.5)
Males	68.2 (12.3)	60.3 (17.8)
Females	70.8 (12.5)	65.4 (16.7)
CLL or NHL as the first malignant primary	26,179 (83.7)	84,248 (86.2)
Duration at risk after first CLL or NHL diagnosis, person-years	4.3 (2.1–7.7)	3.2 (1.0–7.2)

Abbreviations: CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma; SEER, Surveillance, Epidemiology, and End Results.

^aValues are No. of patients (%), mean (SD), or median (interquartile range).^bIncludes small lymphocytic lymphoma.^cDoes not include CLL and small lymphocytic lymphoma.

Table 2

Age- and Sex-Specific Incidence of Subsequent CTCL After CLL or NHL

Sex and Age Strata	CLL Cohort				NHL Cohort			
	Observed CTCL Cases	Incidence per 1,000,000 PY (95% CI)	SIR (95% CI)	P Value	Observed CTCL Cases	Incidence per 1,000,000 PY (95% CI)	SIR (95% CI)	P Value
Female	2	28.1 (3.4–101.3)	1.5 (0.2–5.5)	.74	20	92.0 (56.2–142.1)	5.9 (3.6–9.1)	<.001
0–49 y	0	...	...	...	5	129.8 (42.2–302.4)	40.6 (13.2–94.6)	<.001
50–69 y	0	...	...	...	8	96.4 (41.6–189.8)	6.4 (2.8–12.6)	<.001
70 y	2	46.6 (5.6–167.8)	2.2 (0.3–7.9)	.47	7	73.0 (29.4–150.2)	3.4 (1.4–7.1)	<.001
Male	10	104.2 (50.0–191.8)	3.0 (1.4–5.5)	<.001	23	97.9 (62.0–146.9)	3.7 (2.3–5.5)	<.001
0–49 y	0	...	...	...	2	33.6 (4.1–121.1)	9.5 (1.2–34.3)	.04
50–69 y	5	121.0 (39.3–282.0)	5.5 (1.8–12.8)	.005	11	114.7 (57.4–205.4)	5.2 (2.6–9.3)	<.001
70 y	5	102.5 (33.3–238.9)	2.1 (0.7–4.9)	.19	10	125.7 (60.3–231.3)	2.6 (1.2–4.7)	.002

Abbreviations: CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; NHL, non-Hodgkin lymphoma; PY, person-years; SIR, standardized incidence ratio.

Characteristics of 5 Women Younger Than 50 Years With NHL and Subsequent CTCL

Table 3

Pt	Age at NHL Diagnosis, y	Type of NHL ^a	Site of NHL ^b	Time from NHL to CTCL Diagnosis, y	CTCL Type ^a	CTCL Site ^b
1	37	9714/3: Anaplastic large-cell lymphoma, T-cell and null cell type	C49.3-Connective, subcutaneous, other soft tissue; thorax	5.7	9700/3: Mycosis fungoides	C44.9-Skin, NOS
2	35	9691/3: Follicular lymphoma, grade 2	C02.4-Lingual tonsil	4.8	9709/3: Cutaneous T-cell lymphoma, NOS	C44.6-Skin of upper limb and shoulder
3	37	9591/3: Malignant lymphoma, non-Hodgkin, NOS	C77.9-Lymph node, NOS	0.8	9709/3: Cutaneous T-cell lymphoma, NOS	C44.3-Skin other/unspecified parts of face
4	42	9702/3: Mature T-cell lymphoma, NOS	C77.1-Intrathoracic lymph nodes	0.6	9700/3: Mycosis fungoides	C44.9-Skin, NOS
5	30	9714/3: Anaplastic large-cell lymphoma, T-cell and null cell type	C51.9-Vulva, NOS	7.0	9700/3: Mycosis fungoides	C44.6-Skin of upper limb and shoulder

Abbreviations: CTCL, cutaneous T-cell lymphoma; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; Pt, patient.

^a *International Classification of Diseases for Oncology*, 3rd Edition (ICD-O-3) diagnosis.

^b *International Classification of Diseases for Oncology*, 3rd Edition (ICD-O-3) site.