Increased incidence and recurrence rates of nonmelanoma skin cancer in patients with non-Hodgkin lymphoma: A Rochester Epidemiology Project population-based study in Minnesota

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Background: Cutaneous malignancy is associated with worse outcomes in patients with chronic lymphocytic leukemia (CLL).

Objective: We sought to identify the incidence and recurrence rate of nonmelanoma skin cancer (NMSC) in patients with non-Hodgkin lymphoma (NHL).

Methods: NMSC incidence was calculated and Cox proportional hazards models were used to evaluate associations with risk of recurrence for patients with NHL between 1976 and 2005 who were in the Rochester Epidemiology Project research infrastructure.

Results: We identified 282 patients with CLL or small lymphocytic lymphoma and 435 with non-CLL NHL. The incidence of basal cell carcinoma and squamous cell carcinoma was 1829.3 (95% confidence interval [CI] 1306.7-2491.1) and 2224.9 (95% CI 1645.9-2941.6), respectively, in patients with CLL. The cumulative recurrence rate at 8 years after treatment with Mohs micrographic surgery was 8.3% (95% CI 0.0%-22.7%) for basal cell carcinoma and 13.4% (95% CI 0.0%-25.5%) for squamous cell carcinoma in patients with CLL.

Limitations: This was a retrospective cohort study.

Conclusions: After Mohs micrographic surgery and standard excision of NMSC, patients with NHL had a skin cancer recurrence rate that was higher than expected. Careful treatment and monitoring of patients with NHL and NMSC are warranted. (J Am Acad Dermatol 2015;72:302-9.)

Key words: chronic lymphocytic leukemia; immunosuppression; malignant melanoma; Mohs micrographic surgery.

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common forms of malignancy, with increased incidence in immunosuppressed patients such as those with lymphoma.[1-3] The aggressiveness of nonmelanoma skin cancer (NMSC) in the clinical setting of lymphoma has been shown through increased

Abbreviations used:

BCC:	basal cell carcinoma
CI:	confidence interval
CLL:	chronic lymphocytic leukemia
NHL:	non-Hodgkin lymphoma
NMSC:	nonmelanoma skin cancer
REP:	Rochester Epidemiology Project
SCC:	squamous cell carcinoma

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recurrence rates and increased tumor subclinical extension.[4-7]

The immune system has a role in the development of subsequent neoplasia in patients with lymphoma, with skin cancer being the most common secondary malignancy.[8-10] Although numerous case reports describe the potentially increased aggressiveness of skin cancer in the setting of lymphoma, only 2 case-control studies to date have demonstrated increased recurrence of BCC and SCC in patients with lymphoma.[6,7]

The purpose of this study was to document the incidence and recurrence rates of NMSC in patients with non-Hodgkin lymphoma (NHL) through a population-based approach. In addition, we aimed to identify risk factors that may contribute to the potential aggressiveness of skin cancer in this distinctive patient population.

CAPSULE SUMMARY

- Patients with chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (non-CLL non-Hodgkin lymphoma) have increased nonmelanoma skin cancer incidence.
- Patients with CLL and non-CLL non-Hodgkin lymphoma and with nonmelanoma skin cancer treated surgically had higher recurrence rates, even after Mohs micrographic surgery.
- Prompt and aggressive margin control is necessary to decrease recurrence risk and subsequent skin cancer metastasis.

METHODS

Institutional review board approval was obtained from Mayo Clinic and the Olmsted Medical Center as part of the Rochester Epidemiology Project (REP). REP resources include health care information for Olmsted County, Minnesota, residents from 1966 to the present. The medical records for a given patient are linked together across virtually all Olmsted County health care providers as a part of the REP records linkage system. This allows the health care information for an Olmsted County resident to be monitored continuously, regardless of changes in setting or provider. The medical records of patients identified through REP are shared among Olmsted County health care providers and can be used to identify persons with specific diseases.[11,12] For all patients who resided in Olmsted County as of January 2000, it has been determined that 80% of Olmsted County residents were seen by a REP health care provider at least once within 1 year and 93% were seen within 3 years.[13]

We used the REP research infrastructure to identify patients with diagnosed NHL between January 1, 1976, and December 31, 2005. The disease was defined as the diagnosis of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma, or other forms of NHL. Patients who denied access to their medical records for research purposes were excluded. We reviewed the medical records and abstracted information regarding the diagnosis of secondary neoplasia, including NMSC, either before or after the NHL diagnosis was recorded. Identifying patients with NMSC was done through a diagnostic code search of all medical records in Olmsted County (part of the medical record linkage system of the REP). The presence of an NMSC was further confirmed through the presence of a pathology report, operative report, or both in the patients' medical records. Treatments, tumor histologic type, recurrence, and metastasis were recorded for all NMSC that developed after the NHL diagnosis. The following potential risk factors at the time of the NHL diagnosis were recorded: age, sex, previous tobacco use, and lymphoma treatments.

Statistical analysis

Analyses were performed using software (SAS, Version 9.3, SAS Institute Inc, Cary, NC). *P* values less than .05 were considered statistically significant. Analyses were performed separately for patients with CLL (including small lymphocytic lymphoma) and those with non-CLL NHL. The analysis described herein for BCC outcomes was also conducted separately for SCC outcomes.

For the analysis of BCC incidence, patients were excluded if the BCC was first diagnosed before the date of the NHL diagnosis. A patient's duration of follow-up was calculated from the date of the NHL diagnosis to the date of the first BCC diagnosis, the last follow-up, or death. Age- and sex-specific incidence density estimates were derived from the number of patients with an incident BCC diagnosis relative to the total person-years of observation; values were expressed as incidence per 100,000 person-years.[14] Exact 95% confidence intervals (CI) for the incidence rates were derived by assuming that the observed number of cases followed a Poisson distribution and that the number of person-years was fixed. The cumulative incidence of BCC was estimated with Kaplan-Meier analysis. Cox proportional hazards models were used to evaluate risk factors for their association with development of BCC.

For the analysis of BCC recurrence, all primary BCC tumors of a patient were considered unless