Upper Aerodigestive Tract Cancer in Patients With Chronic Lymphocytic Leukemia

Incidence, Stage, and Outcome

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Objective: To compare incidence, stage, and survival of upper aerodigestive tract (UADT) cancers in patients with and without chronic lymphocytic leukemia (CLL).

Design: Inception cohort.

Setting: National database.

Patients: Individuals with CLL and UADT cancers included in the Surveillance, Epidemiology, and End Results (SEER) database.

Main Outcome Measures: Incidence was compared by computing standardized incidence ratio (SIR), the ratio of observed UADT cancers in patients with CLL, and the number of UADT cancers expected based on the characteristics of patients with CLL and population incidence of UADT cancers. The association between CLL and UADT cancer stage was measured using odds ratio (OR) calculations. Survival of patients with UADT cancer with and without CLL was compared.

Results: For the SIR calculation, 36,985 patients with CLL contributed a mean 6.36 years of follow-up each, for a total of 235,314 person-years of follow-up. The SIR was 1.18 (95% CI, 0.97-1.41) for UADT cancers; 1.52 (95% CI, 1.18-1.93) for laryngeal cancer; and 1.92 (95% CI, 1.05-3.23) for cancers of the nasal cavity and paranasal sinuses. In the stage and survival analyses, 253 patients with CLL followed by a UADT cancer were compared with 133,840 patients with 1 UADT cancer only. Cancers of the UADT in patients with CLL were more likely localized (OR, 0.50; 95% CI, 0.37-0.68). Relative survival was worse in patients with CLL. In multivariate analysis, CLL was independently associated with poorer observed survival (hazard ratio, 1.45; 95% CI, 1.24-1.70).

Conclusions: Larynx and nasal cavity cancers were more common in patients with CLL. Overall incidence of UADT cancers was not significantly elevated. Cancers of the UADT in patients with CLL were more likely to be localized at diagnosis than those in patients without CLL. Finally, CLL was associated with poorer survival outcomes.


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C H R O N I C L Y M P H O C Y T I C L E U K E M I A (CLL) is the most common leukemia in adults in the United States, with an age-adjusted annual incidence of 4.7 per 100,000 men and 2.5 per 100,000 women. The incidence increases with age.1 Immunosuppression is commonly considered a hallmark of CLL. Between 25% and 50% of patients with CLL ultimately die of infection, most frequently involving the respiratory or urinary tracts.2 Small lymphocytic lymphoma is an indolent B-cell malignant condition, which is immunophenotypically identical to CLL but lacks the circulating lymphocytosis seen in CLL. The current World Health Organization classification considers small lymphocytic lymphoma and CLL as a single entity.3,4 Conditions causing immunosuppression are frequently associated with alterations in the behavior of neoplasms. A recent study described changes in cancer incidence in patients who had undergone a solid-organ transplant,5 and human immunodeficiency virus–related cancers have been well described. Chronic lymphocytic leukemia has been studied in this context by Travis et al,6 Hisada et al,7 and Morton et al.6 Ishibe and Curtis,9 using the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database, reported a statistically significant 19% increase in the risk of subsequent primary cancers in patients with CLL, with the lip, larynx, and nasal cavity among the primary sites demonstrating increased risk. Staging and outcomes were not reported in that study.
Data were obtained from SEER using SEER therefore did not require institutional review board approval. This study used deidentified data in a public-use data set and patients with a prior diagnosis of CLL.

METHODS

This study used deidentified data in a public-use data set and therefore did not require institutional review board approval. Data were obtained from SEER using SEER*Stat 7.0.5 software. This database includes comprehensive cancer incidence data in 9 geographic locations (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco/Oakland, Seattle/Puget Sound, and Utah) from 1973 through 2008, in 4 more locations (Los Angeles, San Jose/Monterey, Alaska Natives, and rural Georgia) from 1992 through 2008, and in an additional 4 locations (Kentucky, New Jersey, Louisiana, and greater California) from 2000 through 2008. The 9-registry database covers approximately 10% of the US population, and the full 17-registry database covers approximately 26% of the US population.

We defined CLL and small lymphocytic lymphoma using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) histology codes 9670 and 9823, respectively. Upper aerodigestive tract cancers were defined using ICD-O-3 primary site codes C00.0-C14.8 and C30.0-C32.9. All histologic types at UADT sites were included.

To compare incidence, SEER*Stat software was used to compute standardized incidence ratios (SIRs) for UADT sites from population incidence rates adjusted for age, race, and sex. This inquiry was limited by SEER*Stat to the 9-registry database. The SIR compares the number of observed cases to the number of expected cases. The incidence of UADT cancers in patients with CLL was compared with that in the general population.

RESULTS

During the study period, 36,985 patients were diagnosed as having CLL, with 235,314 person-years of follow-up, representing a mean of 6.36 follow-up years per patient. The resulting SIR data are given in Table 1. The SIR for cancers of all UADT sites was 1.18 (95% CI, 0.97-1.41). In other words, the incidence of UADT cancer was 18% greater in patients with CLL. The SIR for laryngeal cancer was 1.52 (95% CI, 1.18-1.93), and for nasal cavity and paranasal sinus sites, 1.92 (95% CI, 1.05-3.23).

To account for potential changes in incidence of oropharynx cancer related to human papillomavirus, separate SIRs were calculated for the periods 1973 through 1995 and 1996 through 2008. The SIR for oropharynx cancer for the period 1973 through 1995 was 0.91 (95% CI, 0.51-1.49), and in the later period, 0.44 (95% CI, 0.16-0.95). The latter was statistically significant, although with 13.7 oropharynx cancers expected, the sample size was small.

The full 17-registry SEER database contained 253 patients with CLL and a subsequent head and neck cancer. There were 133,840 patients with 1 head and neck cancer and no other cancers. Comparisons of the 2 cohorts are given in Table 2. Patients with CLL were more

<table>
<thead>
<tr>
<th>Site</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All UADT sites</td>
<td>1.18 (0.97-1.41)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>1.07 (0.80-1.39)</td>
</tr>
<tr>
<td>All pharynx</td>
<td>0.75 (0.52-1.05)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>0.69 (0.43-1.06)</td>
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<tr>
<td>Hypopharynx</td>
<td>0.65 (0.28-1.29)</td>
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<tr>
<td>Nasopharynx</td>
<td>1.47 (0.54-3.21)</td>
</tr>
<tr>
<td>Larynx</td>
<td>1.52 (1.18-1.93)</td>
</tr>
<tr>
<td>Nasal cavity/paranasal sinuses</td>
<td>1.92 (1.05-3.23)</td>
</tr>
</tbody>
</table>

Abbreviations: CLL, chronic lymphocytic leukemia; SIR, standardized incidence ratio; UADT, upper aerodigestive tract.

Table 1. Effect of CLL on Incidence of Cancer at UADT Subsites

Methods

The purpose of this study was to describe the effect of CLL on the incidence, stage at diagnosis, and natural history of subsequent cancers of the upper aerodigestive tract (UADT). This study represents the addition of 8 years of data to the work published by Ishibe and Curtis. In addition, we sought to describe the stage at presentation and outcomes of UADT cancers occurring in patients with a prior diagnosis of CLL.
likely to be male and were on average a decade older at the time of diagnosis of UADT cancer. As given in Table 2, the overall distribution of primary sites within the UADT differed between the groups, with the most clinically significant differences being the more frequent laryngeal cancers and less frequent oropharynx cancers in the CLL group. Importantly, these data were in agreement with the SIR data reported in Table 1, which were derived from the 9-registry database.

Also given in Table 2 is the distribution of UADT cancer stage at presentation. Head and neck cancers were less likely to demonstrate regional or distant spread in patients with CLL, with an OR of 0.40 (95% CI, 0.30-0.54) (P < .001). Primary site may well be a confounder in the association between CLL and stage at presentation, so the Mantel-Haenszel OR was calculated. After adjusting for primary site, the OR was 0.50 (95% CI, 0.37-0.68) (P < .001) (Breslow-Day test of homogeneity, P = .58, indicating validity of the adjusted OR).

We used follow-up data to compute actuarial observed survival estimates comparing patients with CLL and those without CLL. The estimates are shown in Figure 1. The survival estimates for the CLL and the non-CLL group were different (log-rank, P < .001). A multivariate Cox proportional hazard model was developed to evaluate the effect of CLL on observed survival. The model also included age, stage, primary site, and year of diagnosis. The results are given in Table 3. The hazard ratio for CLL was 1.45 (95% CI, 1.24-1.70) (P < .001). The proportional hazard assumption was verified (data not shown).

We generated separate relative survival comparisons data for local, regional, and distant cancers. For each stage, the difference in relative survival between the CLL and non-CLL groups was significant (P < .001). The relative survival estimates for local and regional UADT cancers are shown in Figure 2.

These data represent an update of earlier studies with additional data on stage and survival. The inclusion of data from 2000 through 2008 adds significantly to the report of Ishibe and Curtis. Specifically, the latter study included more than 19 000 patients followed for approximately 115 000 person-years. The present report more than doubles the sample size. Two other national registry-based studies have reported standardized incidence ratios for second primary UADT cancers in patients with a history of CLL. Schöllkopf et al, studying the Danish cancer registry, did not identify altered incidence of UADT cancers. Royle and colleagues analyzed second cancers in patients with CLL using an Australian cancer registry and reported an increase in the risk of cancers of...
and regionalized (B) upper aerodigestive tract (UADT) cancer. Patients per year and therefore might be more likely to receive regular follow-up with a medical oncologist 2 to 4 times surveillance bias. Typically, patients with CLL maintain expectation, with UADT cancers more likely to be localized in patients with CLL.

The reasons for the effect of CLL on UADT cancer incidence are not known. Immunosuppression associated with CLL, either intrinsic to the CLL itself or related to the treatments used, is a primary consideration. The UADT sites, which are more susceptible, are not ones typically associated with virally mediated carcinogenesis. In fact, given the incidence findings in the later-period (1996-2008) cohort, there may be a protective effect in the oropharynx, where human papillomavirus is known to be a causative factor. Hisada et al proposed a role for shared risk factors, such as tobacco use, since cancers of the lung occurred at a higher-than-expected rate. However, tobacco use is also a strong risk factor for oral cancer, which was not more likely in patients with CLL.

Our study identified differences in stage at presentation, with UADT cancers more likely to be localized in patients with CLL. A possible explanation for this is a surveillance bias. Typically, patients with CLL maintain regular follow-up with a medical oncologist 2 to 4 times per year and therefore might be more likely to receive referral for evaluation of UADT-related symptoms that might permit earlier diagnosis.

The SEER data set did not permit us to compare how UADT cancers were treated in patients with CLL and in those without CLL. The SEER database provides reliably complete information about surgical treatment and radiotherapy. However, matching chemotherapy information is not available. Without accounting for the use of chemotherapy, it is not possible to usefully compare treatment regimens for UADT cancers or assess the effect of therapy directed at CLL. The relationship between CLL and squamous and basal cell carcinomas of the skin is of interest to head and neck oncologists. That relationship is not described in this study because those common cutaneous malignant conditions are not reported to SEER.

A significant issue facing this group of patients is perioperative morbidity and mortality. Our study does not address this topic. Immunosuppression is frequently considered a powerful risk factor for postoperative wound-healing complications. Unfortunately, the SEER database does not contain variables that would permit assessment of this relevant question. Additional studies involving review of patient medical records would be required to address this important issue.

In conclusion, the experience of UADT carcinoma is different in patients with a history of CLL. Incidence rates are higher than expected in the larynx and in the nasal cavity and paranasal sinuses. Staging data demonstrate a likely surveillance effect, with patients with CLL presenting at earlier stage. Chronic lymphocytic leukemia is an independent risk factor for mortality in patients with UADT cancer.

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Author Contributions: Dr Pagedar had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Pagedar, Halfdanarson, and Hoffman. Acquisition of data: Pagedar and Karnell. Analysis and interpretation of data: Pagedar, Halfdanarson, and Hoffman. Drafting of the manuscript: Pagedar, Halfdanarson, Hoffman, and Funk. Critical revision of the manuscript for important intellectual content: Halfdanarson, Karnell, Hoffman, and Funk. Statistical analysis: Pagedar, Halfdanarson, and Karnell. Study supervision: Hoffman and Funk.

Conflict of Interest Disclosures: None reported.

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REFERENCES