Aggressive Behavior of Cutaneous Squamous Cell Carcinoma in Patients With Chronic Lymphocytic Leukemia

Jonathan M. Tomaszewski, FRANZCR; Haim Gavriel, MD; Emma Link, PhD; Sholeh Boodhun, MBBS; Andrew Sizeland, FRACS; June Corry, FRANZCR

Objectives/Hypothesis: Immunosuppression in organ transplant recipients increases the incidence and aggressiveness of cutaneous squamous cell carcinoma. However, there are little clinical data on cutaneous squamous cell carcinoma in patients with immunosuppression due to chronic lymphocytic leukemia. In this study we evaluated the clinical features, patterns of recurrence, and outcomes of cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia.

Study Design: Retrospective cohort study.

Methods: A review was performed of 42 consecutive patients with cutaneous squamous cell carcinoma and chronic lymphocytic leukemia presenting to our institution between July 2000 and July 2010. Baseline characteristics, treatment details, and outcomes were analyzed.

Results: Thirty-four patients presented with primary cutaneous squamous cell carcinoma (33 node negative, 1 node positive), and eight patients presented with nodal disease without a simultaneous index primary. The 2-year cumulative incidence of local recurrence for primary cutaneous squamous cell carcinoma was 15%. Nodal recurrence occurred in 36% of node-negative patients. The 3-year overall and cause-specific survival rate for all patients was 37% and 65%, respectively. In patients managed curatively for nodal disease at presentation or relapse (n = 17), the 3-year overall and cause-specific survival rate was 21% and 53%, respectively.

Conclusions: Patients with cutaneous squamous cell carcinoma and chronic lymphocytic leukemia experience higher rates of skin cancer recurrence and death than expected in an immunocompetent population. Novel strategies are needed to improve outcomes.

Key Words: Cutaneous squamous cell carcinoma, chronic lymphocytic leukemia, immunosuppression, recurrence, survival.

Level of Evidence: 4.

Laryngoscope, 124:2043–2048, 2014

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is an incurable low-grade hematological malignancy and the most common leukemia in Western societies. The median age of diagnosis is 65 years, there is a male predominance, and Caucasians are at highest risk.1,2 CLL results in an immunosuppressed state as a consequence of both the disease and its treatment.3 Patients with CLL have an increased risk of second malignancies including nonmelanoma skin cancer (NMSC).3–5 Recent Australian population-based data suggest a 17-fold increase in NMSC-related mortality in CLL patients.6

NMSC, predominantly comprising basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC), is the most common malignancy in white-skinned populations, and the incidence is increasing in many countries, including Australia.7 Similar to CLL, elderly Caucasian males are a high-risk group. Chronic ultraviolet radiation exposure is the major etiological factor. Australia has the highest incidence worldwide, with NMSC accounting for more than five times the number of all other cancers combined.8 Cutaneous squamous cell carcinoma typically accounts for 20% of NMSC,9 although the BCC:cSCC ratio is reversed in immunocompromised (organ transplant) patients.10 The majority of NMSC-related morbidity and mortality is due to cSCC.

It is well recognized that immunosuppression in organ transplant recipients not only increases the incidence but also the aggressiveness of cSCC.11,12 However, there are few publications describing the clinical behavior of cSCC in patients with CLL. The aim of this study was to analyze the clinical features, patterns of recurrence, and outcomes of cSCC developing in patients with CLL.
MATERIALS AND METHODS

Hospital records of consecutive patients with cSCC attending a tertiary cancer center and treated curatively for cSCC between July 2000 and July 2010 were retrospectively reviewed. Data collection was approved by the institutional ethics committee. Demographic details, tumor and treatment characteristics, and outcomes were recorded. Details of second and subsequent primary tumors were collected if these were deemed high risk, defined as any of the following features: size >2 cm, poorly differentiated, perineural invasion, deep invasion (into or beyond reticular dermis), positive surgical margins, ear/lip location, or associated with subsequent locoregional or distant recurrence. Cause of death and date of cSCC diagnosis was verified with data from the state cancer registry.

Cutaneous SCC was staged according the American Joint Committee on Cancer staging system (7th edition, 2010). Primary tumor staging was pathological (by surgical excision), or clinical in those patients treated with definitive radiotherapy (RT). Nodal and distant metastatic staging was by physical examination. Routine imaging was only obtained in patients with clinical evidence of nodal or distant disease.

During the study period, the institutional policy for curative management of primary cSCC was surgical excision, with postoperative radiotherapy (PORT) added in patients deemed to be at high risk of local recurrence (e.g., positive margins). Definitive RT was reserved for patients whose age or comorbidities precluded surgery or where the functional or cosmetic outcome was expected to be better with RT. Nodal disease was managed with lymph node dissection, with the addition of PORT for the following indications: 1 or more parotid node, 2 or more neck nodes, 3 or more axilla or groin nodes, extracapsular extension or nodes >3 cm. The RT fields encompassed the primary site when the time interval between the suspected index primary and nodal disease was <12 months. Routine follow-up was with clinical examination alone without routine imaging.

Statistical Analysis

Median follow-up time was defined as the time between the end of treatment for cSCC and the date of last contact or death. Time to local recurrence, cause-specific survival (CSS), and overall survival (OS) from the date of surgery or completion of RT was assessed by the Kaplan-Meier method. Disease-free interval was defined as the time between treatment of primary cSCC and the diagnosis of local or regional nodal recurrence. Local recurrences were based on one tumor per patient. Regional nodal recurrences were scored irrespective of whether the first or subsequent primaries were the suspected source.

RESULTS

Patient and Tumor Characteristics

A total of 42 patients were identified who met the study criteria. As expected, the majority of patients were males over the age of 60 years with cSCC of the head and neck region. Thirty-four patients presented with primary cSCC (33 node negative, one node positive). Perineural invasion status was specifically stated in the pathology report in 19 patients. Microscopic perineural invasion was observed in nine of 19 primaries; it was absent in 10. In the remaining 15 patients, there was no specific comment on perineural invasion in the pathology report. No patients had clinical (symptomatic or radiological) perineural invasion. Eight patients presented with nodal metastases without a simultaneous index primary. Three of the 42 patients (one node positive, two node negative) had in-transit metastases. Patient and tumor characteristics are presented in Table I.

The median time from cSCC diagnosis to presentation for cSCC management was 4.5 years (range, 0–26.5, n = 42). Thirty patients (71%) received systemic therapy for CLL during the study period. The most commonly used agents were fludarabine, cyclophosphamide, rituximab, and chlorambucil, alone or in combination.

Treatment Characteristics

Initial management for all patients is shown in Figure 1. Primary cSCC was managed by surgical excision with standard sectioning in 27 of 34 patients (79%). The remaining seven primaries (21%) were treated with definitive RT, including two patients treated with wide-field scalp irradiation. Of the patients treated surgically, eight (29%) received PORT to the primary site, either due to positive margins (n = 5) or a combination of high risk features (n = 3). One node-negative patient received elective nodal irradiation. All patients presenting with
regional nodal involvement underwent lymphadenectomy, and all met criteria for PORT. Eight of nine received PORT to the nodal basin, including one patient with a simultaneous primary tumor who received PORT to both the nodal basin and primary site. One patient did not receive PORT due to postoperative complications and the early development of distant metastatic disease. The RT technique for primary site irradiation (definitive or postoperative) was electrons in 10 patients, kilovoltage photons in two patients, electron/megavoltage photon mix in two patients, and megavoltage photons in one patient. Doses ranged from 24 Gy in four fractions to 60 Gy in 30 fractions. Nodal basins were treated using megavoltage photons, with the exception of one patient who was treated with en face electrons.

In total, 21 patients either presented with \( n = 9 \) or developed \( n = 12 \) nodal disease during the study period. Seventeen of 21 were managed curatively with lymphadenectomy with \( n = 16 \) or without \( n = 1 \) PORT. The most common RT dose for nodal irradiation was 60 Gy in 30 fractions. Treatment and tumor characteristics for the 17 patients with nodal disease managed with curative intent are shown in Table II. Four patients with recurrent nodal cSCC were managed with palliative intent due to distant metastases \( n = 1 \) or extensive unresectable disease \( n = 3 \).

**Second Primary Tumors**

A total of 99 additional high-risk primary cSCCs occurred in 22 (52%) patients during the follow-up period. The median number of additional high-risk cSCCs was two, with a range of one to 30.

**Patterns of Disease Recurrence and Survival**

In total, excluding new primary cSCC, 20 patients (48%) experienced recurrent disease.

**Local recurrence.** Of the 34 patients with a primary cSCC, six had locally recurrent disease at the time of presentation to our unit. Four of 34 primary tumors (12%) subsequently recurred locally; one of four was a second local recurrence. The 1-year and 2-year cumulative incidence of local recurrence was 9.5% (95% confidence interval [CI], 0–19.2) and 15.2% (95% CI, 0–28.4), respectively. The median disease-free interval was 7.45 months (range, 3–20.4 months). Of the nine patients who presented with or developed local recurrence, three had further local recurrences at the same site, five developed nodal \( n = 3 \) or in-transit metastases \( n = 2 \), and five ultimately died from cSCC.

**Regional nodal recurrence.** Regional nodal recurrence occurred in 12 of 33 (36%) patients who were node negative at presentation. The median disease-free interval was 7.6 months (range, 0.1–20.8 months). A total of 21 patients either presented with or developed nodal disease during the study period. This occurred at a median of 7.2 years (range, 0.1–18.8 years) after the diagnosis of CLL. Of the 17 patients with nodal disease managed with curative intent (Table II), regional recurrence occurred in nine patients (53%) at a median of 1.5 months (range, 0–32.9 months) following the completion.
of treatment. Four of 17 patients (24%) developed distant metastases, and nine of 17 (53%) died from cSCC.

In-transit metastases. In-transit metastases were observed in 10 patients (23%), three at presentation and seven at recurrence. These were most frequently located on the scalp or periauricular region (8/10 patients). Six of 10 patients were treated with curative intent, four patients with surgery followed by PORT, one patient with surgery alone, and the other with wide-field scalp irradiation. At last follow-up, only two patients were rendered free of locoregional disease. Four of 10 patients were treated palliatively in the context of very extensive disease within previously irradiated skin. Seven patients died from cSCC, and three died from complications of CLL.

Distant metastases. Distant metastases occurred in six patients (14%). Four of six patients were node negative at presentation, giving a rate of 12% (4/33 patients) in this subgroup. Distant recurrence was always preceded or accompanied by regional recurrence. Sites of distant disease included lung/pleura (six patients), nonregional lymph nodes (two patients), and bone (one patient). Two patients failed at a combination of distant sites. Median survival following the development of distant disease was 22 days (95% CI, 5–196).

Survival. In total, 37 of 42 patients (88%) died during follow-up. The follow-up times for the five patients alive were 1.7, 2.8, 3.7, 5.6, and 9.5 years. Fifteen patients (36%) died from cSCC, including 11/33 (33%) who were initially node negative. Sixteen patients (38%) died from complications of CLL. The estimated 3-year OS and CSS for the entire cohort (n = 42) was 37% (95% CI, 25–56) and 65% (95% CI, 50–84), respectively (Fig. 2). The estimated 3-year OS and CSS in patients with nodal disease managed curatively was 21% (95% CI, 8–55) and 53% (95% CI, 32–86), respectively (Fig. 3).

**DISCUSSION**

This retrospective analysis of consecutive patients treated over a 10-year period is the largest reported series of patients with cSCC and CLL, and the only series documenting outcomes in patients with nodal disease. It demonstrates the aggressive nature of cSCC in patients with CLL, with a 3-year OS and CSS of only 37% and 65%, respectively. The 2-year cumulative incidence of local recurrence for primary cSCC was 15%, and 36% of node-negative patients experienced nodal recurrence. Patients with nodal disease had particularly poor outcomes, with a regional control rate of 47% and 3-year OS and CSS of only 21% and 53%, respectively. Patients with CLL experienced higher rates of

<table>
<thead>
<tr>
<th>TABLE II. Tumor and Treatment Details for Patients With Nodal Disease Managed With Curative Intent (n = 17).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. (%) or Median [Range]</strong></td>
</tr>
<tr>
<td>Nodal basin</td>
</tr>
<tr>
<td>Parotid</td>
</tr>
<tr>
<td>Neck</td>
</tr>
<tr>
<td>Parotid and neck</td>
</tr>
<tr>
<td>Axilla</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Largest node, mm</td>
</tr>
<tr>
<td>Extracapsular extension</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Number of involved nodes</td>
</tr>
<tr>
<td>AJCC N stage</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2a</td>
</tr>
<tr>
<td>N2b</td>
</tr>
<tr>
<td>Nx*</td>
</tr>
<tr>
<td>PORT</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>RT alone</td>
</tr>
<tr>
<td>RT + chemotherapy</td>
</tr>
<tr>
<td>Radiotherapy dose, Gy</td>
</tr>
<tr>
<td>Days between surgery and PORT</td>
</tr>
</tbody>
</table>

*Node positive, but the size of the largest node not assessed.
AJCC = American Joint Committee on Cancer; PORT = postoperative radiotherapy; RT = radiotherapy.

Laryngoscope 124: September 2014

Tomaszewski et al.: Cutaneous SCC in Patients With CLL
recurrence and death from cSCC than would be expected in an immunocompetent population.

Prognosis of primary cSCC depends on many factors including tumor size, grade, depth of invasion, and location. However, for patients without nodal disease, the prognosis is generally excellent. In a prospective study of 615 patients with primary cSCC (95% immunocompetent), the rates of local recurrence and regional metastasis were 3% and 4%, respectively.13 With a median follow-up of 43 months, only 9/615 (1.5%) patients died from metastatic cSCC.

A prospective study from the M. D. Anderson Cancer Center included cSCC patients more representative of those referred to a specialized cancer center.14 The proportion of immunosuppressed patients was not reported. Among 210 patients, almost one-quarter of primary tumors were locally recurrent, and 13% of patients presented with nodal disease. The OS and CSS for the entire cohort at 3 years was 70% (95% CI, 62–79) and 85% (95% CI, 78–92), respectively.

A prospective study from the M. D. Anderson Cancer Center included cSCC patients more representative of those referred to a specialized cancer center.14 The proportion of immunosuppressed patients was not reported. Among 210 patients, almost one-quarter of primary tumors were locally recurrent, and 13% of patients presented with nodal disease. The OS and CSS for the entire cohort at 3 years was 70% (95% CI, 62–79) and 85% (95% CI, 78–92), respectively.

The development of nodal metastases is associated with a poorer prognosis in patients with cSCC. Multiple nonrandomized series demonstrate an approximate 70% to 75% regional control and CSS in patients with parotid and/or cervical lymph node metastases treated with surgery and PORT.15 Outcomes vary depending on the size and number of involved nodes.16 The prognosis of metastatic nodal disease in immunosuppressed patients seems to be particularly poor,17–20 but the clinical course in the context of CLL has not previously been described.

Our data demonstrate the ominous prognosis of nodal metastases from cSCC in patients with CLL despite aggressive management with surgery and PORT. In a recent large Australian series of patients with nodal disease treated with surgery ± PORT, 92/603 patients (15%) died from cSCC.21 This compares with 9/17 patients (53%) in this CLL population.

A review of the literature to date shows the evidence for poorer outcomes of cSCC in patients with CLL is largely limited to case reports and small case series of <10 patients.22–25 A clinicopathologic study of 12 consecutive patients with cSCC and CLL suggested that cSCCs in the context of CLL are often multiple and high grade, with a tendency for local and regional recurrence.26 One larger series (n = 28) from the Mayo Clinic demonstrates an increased risk of local recurrence in patients with CLL undergoing surgically for nonmetastatic cSCC when compared to a matched control group.27 An increased risk of metastasis and mortality in the CLL cohort was also reported, although this was based on a very small number of events (three in the CLL group vs. none in the control group).28

The poor prognosis of cSCC in patients with CLL demonstrated in this study highlights the need for further studies investigating intensification of therapy. Recognition of the elevated risk and aggressive nature of cSCC in organ transplant recipients has led to the publication of consensus guidelines aiming to minimize morbidity and mortality in this population.29,30 It would seem from the results of our study that a similarly comprehensive multidisciplinary approach to prevention, early detection, and aggressive management of cSCC in patients with CLL is warranted.3 Education about sun protection and early detection, and proactive management of field cancerization should be initiated at the time of diagnosis of CLL.

The 15% rate of local recurrence observed in this series is higher than expected in an immunocompetent population (<10%).13,31 However, this may reflect the higher-risk cSCCs seen at a tertiary cancer center rather than the presence of CLL per se. The low number of events in our cohort precludes analysis of predictive factors. Notably, six of the 34 patients with primary cSCC were referred with locally recurrent disease. Mohs micrographic surgery is not in routine use at our institution but is considered by some to be the optimal approach to high-risk cSCC.30 In the context of CLL, resection of an additional margin has been suggested after Mohs surgery to reduce the likelihood of false-negative margins due to discontiguous tumor spread.27 When definitive or postoperative RT is utilized, the frequency of in-transit metastases in our study supports the use of generous RT field margins.

Many of the patients in this series had multiple primary cSCCs, sometimes in catastrophic numbers. Oral retinoids (e.g., acitretin) can reduce the incidence of new primary cSCCs in organ transplant recipients30 and may have a role in patients with CLL.

The high rate of early nodal recurrence in this study points to the importance of adequate staging in patients...
with cSCC and CLL. Computed tomography (CT) is more sensitive than physical examination for the detection of lymphadenopathy, and should be considered for staging high-risk primaries in patients with CLL. Central necrosis and irregular contrast enhancement on CT may assist in differentiating metastatic cSCC from any underlying CLL nodal involvement. Positron-emission tomography-CT might further aid with this distinction. Sentinel lymph node biopsy might improve detection of microscopic nodal involvement but is currently investigational. Given the high rate of nodal metastases and the poor nodal control rate despite multimodality treatment, consideration should also be given to treating the draining nodal station(s) prophylactically in patients with high-risk primary cSCCs requiring PORT.

Our data demonstrate a clear need to improve outcomes of nodal cSCC in patients with CLL. Novel approaches to intensifying treatment for high-risk cSCC in nonimmunocompromised patients are currently under investigation. These include the addition of concurrent chemotherapy to PORT (as in the Trans-Taskman Radiation Oncology Group POST trial). Another approach is incorporating epidermal growth factor receptor inhibition in the neoadjuvant or adjuvant setting.

CONCLUSION

Patients who develop cSCC on a background of CLL experience high rates of skin cancer-related morbidity and mortality. Results with current standard treatment regimens are poor, highlighting the need for prospective studies utilizing novel management strategies. International collaboration will be required given the rarity of this patient group.

BIBLIOGRAPHY


