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Review

Cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia: a systematic review of the literature

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Abstract

The continuous improvement of life expectancy of patients with chronic lymphocytic leukemia (CLL) has resulted in increased risk of second primary malignancy that potentially may affect survival and quality of life of CLL patients. We performed a systematic review to assess the risk and the clinical-pathological features and prognosis of cutaneous squamous cell carcinoma (cSCC) in patients with CLL. We searched PubMed, Embase, and Cochrane Central Register of Control Trials databases for articles published from database inception to December 31, 2019. English-language studies reporting original data on patients with a specific diagnosis of CLL and cSCC were included. Data were extracted using a standardized extraction form, and any discordance was resolved by consensus. Descriptive data were generated by pooling patients from eligible studies. Of the 4588 non-duplicate records identified, 55 articles met our inclusion criteria. These studies reported that CLL patients have a 3.2% prevalence of cSCC, with an 11.5% cSCC-related lethality and an overall risk of metastasis of 5.7% (7.3% for regional lymph node involvement and 3.8% for distant metastasis). The quality of evidence was limited by the high heterogeneity in the design, populations, and objectives of the included studies. This systematic review suggests that cSCC in CLL patients tends to behave less aggressively compared with the solid organ transplant recipients but has a higher morbidity and mortality than in the general population. Future prospective studies are needed to increase the quality of evidence and to determine the best treatment modalities and screening intervals for these patients.

Introduction

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder characterized by the progressive accumulation of functionally incompetent monoclonal B lymphocytes in peripheral blood. CLL is the most common form of leukemia in adults in the Western world, with an annual incidence rate of five cases per 100,000 individuals, a male predominance, and a median age at diagnosis of 70 years.[1] Although the spectrum of clinical presentations ranges from indolent form not requiring treatment to rapidly progressing disease, most patients have a favorable prognosis with a 5-year survival of approximately 85%.[2] Patients with CLL have an immunosuppressed status due to the intrinsic nature of the disease, its treatment, or both.[3]

There is a well-established association between immunosuppression in solid organ transplant recipients (SOTRs) and the increased risk of secondary malignancy, skin cancer above all, with a higher risk of adverse outcome. Unlike the general population, where the most common cutaneous malignancy is basal cell carcinoma (BCC), in SOTRs the incidence of cutaneous squamous cell carcinoma (cSCC) is the highest, and the BCC: SCC ratio is reversed.[4–6] These patients have a 65–250 times increased incidence of cSCC that tends to have an aggressive biologic behavior, with increased rates of recurrence,

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metastasis, and death compared with immunocompetent patients.[4,6–8] Although still very high, the risk of cSCC in OTR seems to be decreasing, which suggests that cSCC risk may be lower in OTR treated with the modern immunosuppressive drugs and that cSCC preventive measures may be effective.[9]

The continuous improvement of survival rates of CLL patients, related to more efficient treatment, increases the likelihood of second primary malignancies (SPMs) such as cSCC that potentially may affect survival and quality of life.[10–12] Thus, it is of fundamental importance to understand the impact of SPMs on survival rate of primary cancer with relatively good prognosis, like CLL. The aim of this systematic review is to analyze the prevalence, clinical-pathological features, and prognosis of cSCC in patients with CLL.

Methods

Search strategy and selection criteria

We conduct this systematic review according with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analyses of Observational Studies in Epidemiology (MOOSE) reporting guidelines, to investigate the association between CLL and cSCC.[13,14] We performed our systematic search in Pubmed, Embase, and Cochrane Central Register of Controlled Trials databases from database inception until Decemeber 31, 2019.

Our search criteria for PubMed were as follows: ("chronic lymphocytic leukaemia" [All Fields] OR "chronic lymphocytic leukemia" [All Fields] OR "leukemia, lymphocytic, chronic, b-cell" [MeSH Terms] OR leukemia [All Fields] OR leukaemia [All Fields]) AND ("carcinoma, squamous cell" [MeSH Terms] OR squamo* [All Fields] OR spino* [All Fields]).

Our search criteria for Embase and the Cochrane Register were as follows: ("chronic lymphocytic leukaemia" OR "chronic lymphocytic leukemia" OR leukemia OR leukaemia) AND (squamo* OR spino*). Moreover, we manually searched the reference list of the included articles to identify additional articles that met our inclusion criteria.

Eligible studies were English-language articles, prospective or retrospective studies, clinical trials, case series, and case reports, describing original data on patients of any age with a specific diagnosis of CLL and cSCC.

Data analysis

Three of us (L.C., G.O., and A.P.) independently performed the search, the title/abstract screening, and extracted data using a standardized extraction form. Any discordance or uncertainty was resolved by consensus. For each study, the reviewer recorded the following variables: characteristics of study (type of publication, year, and study design), number of patients enrolled, and demographics (age and gender), first diagnosis (CLL first, cSCC first, or both diseases at onset), mean time from CLL to cSCC diagnosis, mean follow-up after SCC diagnosis, death from cSCC, death from CLL progression after cSCC diagnosis, characteristics of CLL (age at disease onset, sex, clinical stage, previous treatment), characteristics of cSCC (anatomical site, risk factors, histopathological features, number of lesions, nodal or distant metastasis, local recurrence after therapy, metastasis of SCC to CLL-infiltrated lymph node, previous treatment). In case of missing information, only complete data were considered for statistical analysis. Standard descriptive statistics were used to summarize the data. Descriptive data, expressed in mean values or percentages, were generated by pooling patients from eligible studies. Statistical analyses were performed using the IBM SPSS 26.0 package (IBM SPSS Statistics for Windows, Version 26.0, Armonk, NY: IBM Corp).

Moreover, the reviewers performed quality assessment using an arbitrarily modified version of the Newcastle-Ottawa Scale (NOS) for observational studies in order to assess the quality of case series and case reports.[15]

Results

Literature search

The database search identified 6205 publications. After duplicates removal, 4588 titles and abstracts were reviewed; 4509 studies that did not meet our inclusion criteria were excluded. Further 24 publications were excluded after full-text review. The study selection process is illustrated in Figure 1.

The included 55 papers were published between 1977 and 2019,[16–69] of these 25 (45.5%) during the last decade as described in Table 1; most of the included articles were retrospective studies (30, 54.5%), while the remaining were case series or case reports (25, 45.5%) (Table 1).

Forty-two articles[16–25,27–29,33–36,39,41–48,50–53,55,58–66,68,69] reported cases of cSCC developed after the diagnosis of CLL, nine studies[17,31,32,38,40,49,56,67,70] described the simultaneous diagnosis of both diseases, and 10 papers[18,26,30,37,54,56,57,62,68,69] reported cSCC diagnoses preceding CLL onset. Of note, 13/55 articles reported cases belonging to more than one of the aforementioned categories (Table 1).[17,18,31,32,38,40,49,56,62,67–70] Since in the vast majority of patients included in this systematic review the diagnosis of CLL preceded the development of cSCC, our analysis focuses predominantly on this subset, albeit for the sake of completeness, we report the finding of all three categories. Due to the heterogeneity and poor quality of studies, we did not do a quantitative synthesis of data.

CLL as the first diagnosis

Forty-two articles, including 38807 patients affected by CLL, reported subsequent onset of cSCC.[16–25,27–29,33–36,39,41–48,50–53,55,58–66,68,69]

To calculate the prevalence of cSCC in this population, we further excluded two studies (including a total of 19384 CLL

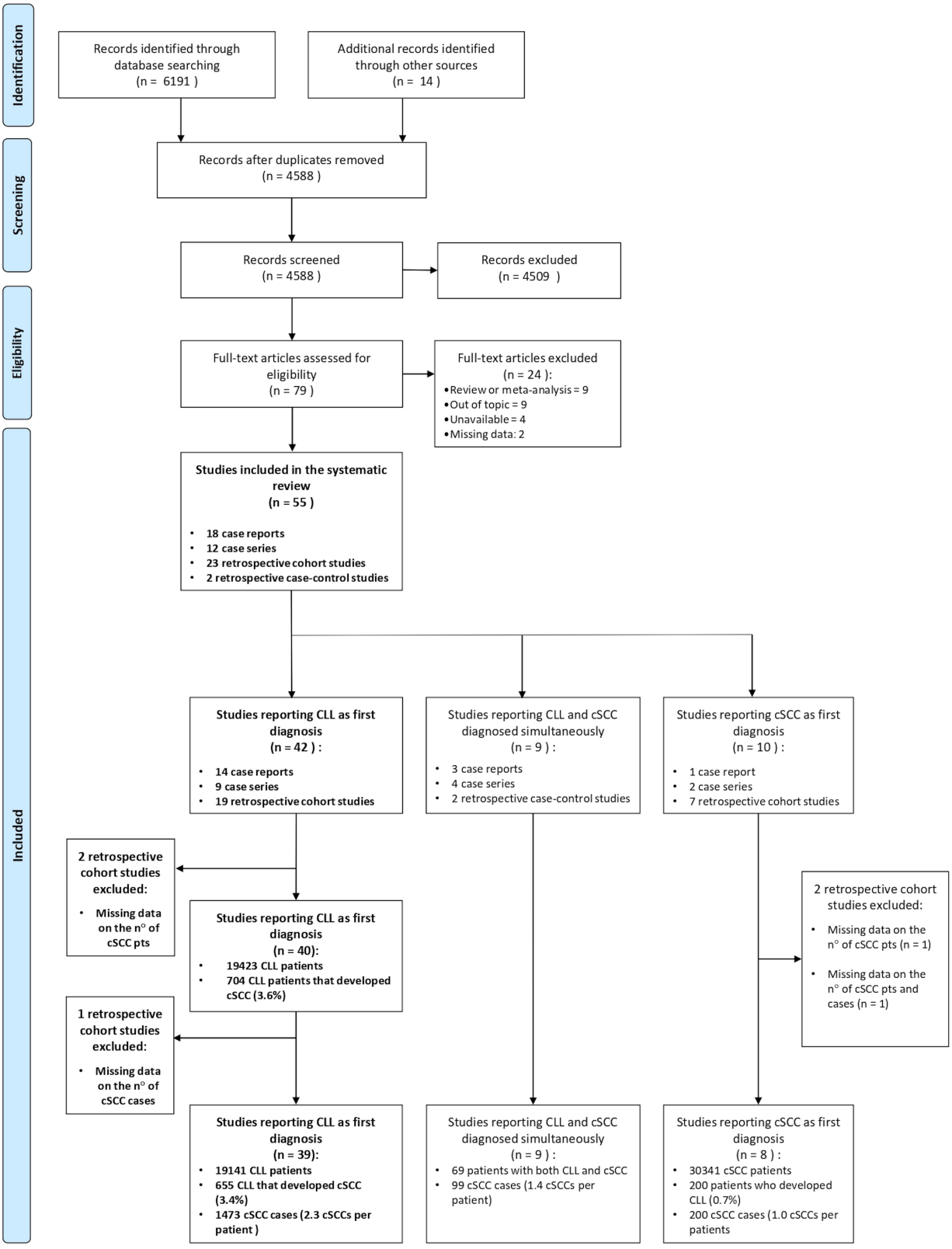

Figure 1 Flow chart of search results and study selection

Table 1 Summary of the 55 studies included in the systematic review

	Year of study	Country	Study type	First occurrence	Study quality[a]
Villet WT *et al.*[16]	1977	South Africa	Case report	CLL first	1
Weimar VM *et al.*[17]	1979	USA	Case series	CLL first and simultaneous CLL and cSCC	1
Mora, RG[28]	1985	USA	Case report	CLL first	1
Bridges N *et al.*[39]	1986	USA	Case report	CLL first	1
Lishner M *et al.*[50]	1987	Israel	Case series	CLL first	2
Perez-Reyes N, Farhi DC.[61]	1987	USA	Retrospective cohort study	CLL first	2
Frierson HF *et al.*[66]	1988	USA	Retrospective cohort study	CLL first	2
Soares FA *et al.*[67]	1992	Brazil	Case report	Simultaneous CLL and cSCC	1
Adami J *et al.*[68]	1995	Sweden, Denmark	Retrospective cohort study	CLL first and cSCC first	2
Hartley BEJ *et al.*[69]	1996	UK	Case series	CLL first and cSCC first	1
Levi F *et al.*[18]	1996	Switzerland	Retrospective cohort study	CLL first and cSCC first	2
Davidovitz Y *et al.*[19]	1997	Israel	Case report	CLL first	1
Dargent JL *et al.*[20]	1998	Belgium	Case report	CLL first	1
Albregts T *et al.*[21]	1998	USA	Case report	CLL first	1
Smoller BR *et al.*[22]	1998	USA	Case series	CLL first	1
Gray Y *et al.*[23]	2001	USA	Case report	CLL first	1
Smith KJ *et al.*[70]	2001	USA	Case series	Simultaneous CLL and cSCC	1
Pigeaud-Klessens ML *et al.*[24]	2002	Netherland	Case report	CLL first	1
Larsen CR *et al.*[25]	2002	Denmark	Case series	CLL first	1
Padgett JK *et al.*[26]	2003	USA	Case report	cSCC first	1
Agnew KL *et al.*[27]	2004	UK	Retrospective cohort study	CLL first	2
Rashid K *et al.*[29]	2005	USA	Case series	CLL first	1
Sheahan P *et al.*[30]	2005	Ireland	Retrospective cohort study	SCC first	2
Mehrany K *et al.*[31]	2005	USA	Retrospective case–control study	Simultaneous CLL and cSCC	2
Mehrany K *et al.*[32]	2005	USA	Retrospective case–control study	Simultaneous CLL and cSCC	2
Flezar MS *et al.*[33]	2006	Slovenia	Case series	CLL first	1
Goh MSY[34]	2006	Australia	Case series	CLL first	1
Wong J. *et al.*[35]	2008	Canada	Case report	CLL first	1
Peng Y *et al.*[36]	2009	USA	Case report	CLL first	1
Toro JR *et al.*[37]	2009	USA	Retrospective cohort study	cSCC first	3
Hodges S. *et al.*[38]	2010	UK	Case report	Simultaneous CLL and cSCC	1
Wilson ML *et al.*[40]	2010	USA	Case series	Simultaneous CLL and cSCC	1
Tomaszewski JM *et al.*[41]	2014	Australia	Case series	CLL first	1
Mansfield AS *et al.*[42]	2014	USA	Retrospective + prospective cohort study	CLL first	2
Velez NF *et al.*[43]	2014	USA	Retrospective cohort study	CLL first	3
Brewer JD *et al.*[44]	2014	USA	Retrospective cohort study	CLL first	3
Tomaszewski JM *et al.*[45]	2014	Australia	Retrospective cohot study	CLL first	3
Dos Santos HT *et al.*[46]	2015	Brazil	Case report	CLL first	1
Vyas R *et al.*[47]	2015	USA	Case report	CLL first	1
Gaide O *et al.*[48]	2016	Switzerland	Case report	CLL first	1
Wollina U *et al.*[49]	2016	Germany	Case report	Simultaneous CLL and cSCC	1
Hock BD *et al.*[51]	2016	New Zealand	Retrospective cohort study	CLL first	2
Kader I *et al.*[52]	2016	Australia	Retrospective cohort study	CLL first	2
Penne M *et al.*[53]	2017	USA	Retrospective cohort study	CLL first	3
Hirshoren N *et al.*[54]	2017	Australia	Case series	cSCC first	3
Hampras S.S *et al.*[55]	2017	USA	Retrospective cohort study	CLL first	3
Callaghan DJ *et al.*[56]	2018	USA	Case series	cSCC first and simultaneous CLL and cSCC	1
Wee E *et al.*[57]	2018	Australia	Retrospective cohort study	cSCC first	2
Walz JS *et al.*[58]	2018	Germany	Retrospective cohort study	CLL first	3

Table 1 Continued

	Year of study	Country	Study type	First occurrence	Study quality[a]
Rausch CR, Kontoyiannis DP[59]	2019	USA	Case report	CLL first	1
Purcell RV *et al.*[60]	2019	New Zealand	Retrospective cohort study	CLL first	3
Zheng G *et al.*[62]	2019	Sweden	Retrospective cohort study	CLL first and cSCC first	2
Inda JJ *et al.*[63]	2019	USA	Retrospective cohort study	CLL first	2
Thiesen I *et al.*[64]	2019	Germany	Retrospective cohort study	CLL first	2
Wu PA *et al.*[65]	2019	USA	Retrospective cohort study	CLL first	2

CLL, chronic lymphocytic leukemia; cSCC, cutaneous squamous cell carcinoma; UK, United Kingdom; USA, United States of America.
[a]Based on Newcastle–Ottawa scale modified for case series and case reports: 1(worse) to 4 (better).

patients),[55,62] since only the number of cSCC was reported and not the number of patients coaffected by CLL and cSCC.

In these 40 studies, a total of 704 out of 19,423 (3.6%) CLL patients developed at least one cSCC.

To calculate the total number of cSCC cases and the mean number of cSCC per patient, another article was then excluded, accounting for 282 CLL patients, in which only the number of patients developing cSCC was provided (*n*: 49) but not the total number of cSCCs.[44]

Thirty-nine articles were thus finally considered, including 655/19141 patients developing cSCC after CLL diagnosis for a total number of 1473 cSCCs (average number of cSCC per patient 2.3) (Fig. 1).[16–25,27–29,33–36,39,41–43,45–48,50–53,58–61,63–66,68,69] Moreover, to calculate the prevalence of cSCC after CLL diagnosis, we excluded case reports and case series in order to avoid overestimation and 16 articles including 612/19,015 patients developing cSCC after CLL diagnosis were finally considered.[18,27,42,43,45,51–53,58,60,61,63–66,68] The prevalence of cSCC after CLL diagnosis was 3.2%, and the average number of cSCC per patient was 2.3.

cSCC-related deaths for patients first diagnosed for CLL were 41/356 (lethality rate: 11.5%) and were reported in 18 studies.[17,21,23–25,28,29,33,35,39,43,45,47,59,61,63,66,69]

The population characteristics of the 39 finally included studies are summarized in Table 2. The mean age of CLL patients who developed a cSCC was 72.9 years (SD ± 2.5, range 44–83), with a male predominance (84.3%). The mean time from CLL onset to cSCC diagnosis was 6.1 years, and 52% of patients developed more than one lesion. In 416 of 713 (58.3%) patients, the cSCC was located on the head and neck region.

Concerning histopathological features of cSCC in CLL patients, 25 of 41 (61%) lesions were invasive and 16 (39%) were in situ; 268 of 398 (67.3%) cSCC were well-differentiated, 70 of 398 (17.6%) moderately differentiated, and 60 of 398 (15.1%) poorly differentiated. Perineural invasion was reported in 24/177 (13.6%) cSCC. Seventeen (3%) locally advanced cSCC were reported in 14 studies including 572 lesions; nodal metastasis was detected in 77 of 1056 (7.3%) cases, and distant metastasis developed in 28 of 783 (3.6%) cases. Local recurrence of cSCC after treatment occurred in 61 of 1041 (5.9%) cases. In eight of 22 (36.4%) cases, metastatic cells of cSCC were detected in CLL-infiltrated lymph nodes.

Due to the poor quality and incompleteness of data, it was impossible to evaluate the correlation between cSCC features and CLL clinical stage or previous/ongoing specific treatment.

Regarding the diagnosis of other cutaneous malignancies in association with cSCC in CLL patients, the included articles reported 14 melanomas, nine BCC, two Merkel cell carcinomas, and two sebaceous carcinomas.

CLL and cSCC diagnosed simultaneously

A total of nine articles reported the simultaneous diagnosis of CLL and cSCC in 69 patients, with a total number of 99 cSCC lesions (average number of cSCC per patient: 1.4), all located on the head and neck region.[17,31,32,38,40,49,56,67,70] The mean age of patients was 73.3 years (SD 5.4; range 60–88); 60 were males (87%) and nine females (13%). The CLL and cSCC characteristics are reported in Table 2.

cSCC as the first diagnosis

Concerning patients first diagnosed with cSCC who subsequently developed CLL, 10 studies were first identified.[18,26,30,37,54,56,57,62,68,69] However, one study was excluded because neither the total number of cSCC lesions nor the number of cSCC patients were provided (including 414 patients with both CLL and cSCC).[62] Another study was also excluded (including 202 SCC patients, of these two with CLL)[30] because the total number of cSCC lesions was not reported.

Eight studies were thus finally considered, including 30,341 cSCC patients, 200 of which subsequently diagnosed for CLL.[18,26,37,54,56,57,68,69] The total number of cSCC in patients coaffected by CLL was 200 (average number of cSCC per patient: 1.0). After the exclusion of case reports/series (four studies including 67 cSCC patients, 14 of these with a subsequent diagnosis of CLL),[26,54,56,69] the prevalence of CLL in cSCC patients was 0.72%. The time from cSCC to CLL diagnosis was only reported for one patient and was 5 years.[56] More data on patients developing CLL after cSCC diagnosis are reported in Table 2.

Table 2 Demographics and cutaneous squamous cell carcinoma (cSCC)-related features of patients with both chronic cell leukemia (CLL) and cSCC

		CLL diagnosis first		**CLL & cSCC simultaneous**		**cSCC diagnosis first**	
		655 patients with 1473 cSCCs (39 studies)		**69 patients with 99 cSCCs (9 studies)**		**200 patients with 200 cSCCs (8 studies)**	
Variables		**value**	**%**	**value**	**%**	**value**	**%**
Mean age ± SD		72·9 ± 2·5	on 343 patients	73·3 ± 5·4	on 69 patients	69·0 ± 0·0	on 1 patient
Sex	Female	77/490	15·7	9/69	13·0	0/3	0·0
cSCC location	Head and Neck	416/713	58·3	99/99	100·0	14/14	100·0
cSCC histology	Invasive	25/41	61·0	0/5	0·0	1/1	100·0
	Grade 1 (well differentiated)	268/398	67·3	22/41	53·7	1/1	100·0
	Grade 2 (moderately differentiated)	70/398	17·6	16/41	39·0	0/1	0·0
	Grade 3 (poorly differentiated)	60/398	15·1	3/41	7·3	0/1	0·0
	Keratoacanthoma	1/41	2·4	0/5	0·0	0/1	0·0
	Perineural invasion	24/177	13·6	1/4	25·0	0/1	0·0
	Cutaneous CLL infiltrates around cSCC	33/97	34·0	5/6	83·3	3/53	5·7
cSCC features	Patients with more than 1 cSCC	75/144	52·1	29/37	78·4	0/1	0·0
	Locally advanced	17/572	3·0	0/6	0·0	0/1	0·0
	Regional lymph node metastasis	77/1056	7·3	5/13	38·5	1/1	100·0
	Distant metastasis	28/783	3·6	5/39	12·8	2/2	100·0
	Recurrence after therapy	61/1041	5·9	9/64	14·1	1/2	50·0
	Metastasis of cSCC to CLL-infiltrated lymph node	8/22	36·4	3/7	42·9	0/1	0·0
cSCC therapy	Cryotherapy	1/83	1·2	0/6	0·0	0/2	0·0
	Laser therapy	1/83	1·2	0/6	0·0	0/2	0·0
	Diathermocoagulation	2/83	2·4	0/6	0·0	0/2	0·0
	5-fluorouracil	1/83	1·2	0/6	0·0	0/1	0·0
	Imiquimod	0/83	0·0	5/6	83·3	0/1	0·0
	Photodynamic therapy	0/83	0·0	0/6	0·0	0/1	0·0
	Radiotherapy	31/228	13·6	0/6	0·0	1/2	50·0
	Chemotherapy	2/19	10·5	0/6	0·0	0/0	0·0
	Surgery	133/281	47·3	5/11	45·5	13/14	92·9
	Mohs Micrographic Surgery	12/90	13·3	58/93	62·4	4/54	7·4
	Post-surgery radiotherapy	30/209	14·4	1/7	14·3	13/14	92·9
	Elective node irradiation	10/164	6·1	1/6	16·7	1/1	100·0
	Nodal dissection	36/182	19·8	2/8	25·0	1/1	100·0
Other skin cancer associated with cSCC in CLL patients	Melanoma with cSCC	14/198	7·1	0/0	0·0	0/0	0·0
	BCC with cSCC	9/26	34·6	9/29	31·0	0/0	0·0
	Merkel cell carcinoma with cSCC	2/184	1·1	0/0	0·0	0/0	0·0
	Sebaceous carcinoma with cSCC	2/69	2·9	0/0	0·0	0/0	0·0
Deaths	from cSCC-related	41/356	11·5	4/34	11·8	1/2	50·0
	CLL-related after cSCC diagnosis	3/22	13·6	1/6	16·7	0/1	0·0

BCC, basal cell carcinoma; CLL, chronic lymphocytic leukemia; cSCC, cutaneous squamous cell carcinoma; SD, standard deviation.

Discussion

The results of our systematic review suggest that CLL patients have a high prevalence of cSCC that tends to behave more aggressively compared with the general population.[10,31,45,51,71] Thus, the development of a second cancer in this subset of patients represents a considerable clinical burden. Based on our data, 3.2% of CLL patients developed a subsequent cSCC. Several epidemiologic studies have reported a 1.86 to 8.6 increased risk of cSCC in patients with CLL.[37,51,62,68] Studies using cancer registries data from Denmark and Sweden have reported an overall relative risk of cSCC of 8.6 (95% CI 7.2–

10.3), increasing with time during the first decade after CLL diagnosis[68]; a more recent study has identified a relative risk of 24.58 for in situ and 7.63 for invasive cSCC.[62] It might be speculated that this high rate of cSCC could result from the higher level of surveillance and diagnosis in this subset of patients. However, one study performed at Mayo Clinic contradicted this hypothesis documenting a low compliance with skin cancer screening in patients with CLL.[42] Nevertheless, it is likely that the true incidence and prevalence of cSCC are underestimated since many countries' cancer registries do not document cSCC.

Regarding patient and tumor characteristics, most of the CLL patients who developed a subsequent cSCC were male with a mean age of 72.9 years, and the most common location of the skin cancer was the head and neck region. These features are in line with data reported in the general population.[72]

Interestingly, SOTRs with cSCC have different clinicopathological traits compared with CLL patients. In contrast to SOTRs, CLL patients developing cSCC seem to be older (72.9, range 44-83 vs. 62, range 36–77), data expected due to overall older age of CLL patients compared with SOTRs, and tend to have cSCC with a lower T stage (39% vs 2% in situ), a higher grade of differentiation of the lesions (67.3% vs 2% well-differentiated; 15.1% vs 41% poorly differentiated), a lower rate of perineural invasion (13.6% vs 39%), and a lower rate of local recurrence (5.9% vs 45%).[73]

Noteworthy, on histopathological examination more than one-third of cSCC in CLL patients are associated with a dense leukemic infiltrate that can complicate histopathologic interpretation especially on frozen section during Mohs micrographic surgery (MMS).[32] This finding may explain why CLL patients are by far more likely to develop recurrence after MMS compared with the general population (local recurrence rate of 13% in CLL patients vs. 3% rate observed in the general population).[44]

Notably, our data show an 11.5% cSCC-related lethality in patients with CLL and an overall risk of metastasis of 5.7% (7.3% for regional lymph node involvement and 3.8% for distant metastasis). To the best of our knowledge, only one study evaluated the impact of cSCC to the overall mortality of CLL patients.[43] More specifically, the authors found that CLL patients had 12–13% risk of death from skin cancer, and the predictors of poor outcome were the following: a high Rai stage at the time of the first skin cancer diagnosis and the occurrence of cSCC with high T stage.

Due to the poor quality and incompleteness of data, it was impossible to evaluate a potential correlation between CLL clinical stage and the development and features of cSCC. A study from the Boston group evaluating the impact of Rai stage on the outcome of skin cancer found that, in a multivariate analysis, advanced Rai stage (III or IV) and high skin cancer tumor (T) stage are significantly associated with poor skin cancer outcome. Thus, the authors suggest that, even though high-T-stage cSCC is associated with a poor outcome regardless of the CLL stage, the Rai stage may be useful in stratifying the risk of patients with low T stage skin cancer.[43] Furthermore, a recent study evaluating the effectiveness of tumor risk stratification of four different tumor staging systems for cSCC (American Joint Committee on Cancer seventh edition and eighth edition, Union for International Cancer Control eighth edition, and Brigham and Women's Hospital staging systems) has suggested that the Brigham and Women's Hospital system provides a superior risk stratification of cSCC tumors in patients with CLL.[63]

Our results do not shed light on the impact of chemoimmunotherapy and irradiation used to treat CLL on the development of secondary malignancy. Existing data suggest that chemoimmunotherapeutic agents, such as fludarabine, chlorambucil, cyclophosphamide, and rituximab, increase the susceptibility to second cancer.[12,19,29,53,71] Further studies are needed to evaluate the possible oncogenic role of classical CLL treatments and recent drugs such as BTK inhibitors, PI3K inhibitors, and BH3-mimetics.[74]

In this systematic review, we also included articles reporting the simultaneous diagnosis of cSCC and CLL.[17,31,32,38,40,49,56,67,70] In these studies, the presence of a dense tumor-associated lymphocytic infiltrate in patients with no history of leukemia represented a clue to the prompt evaluation for the underlying hematologic malignancy. Few studies analyzed the bi-directional relationship between CLL and cSCC.[18,62,68] Further studies are needed to evaluate the impact of non-melanoma skin cancer on the subsequent onset of CLL as the possibility that subclinical CLL may be present at the time of SCC diagnosis should be addressed.

The pathogenesis of leukemia-associated skin cancer is still unknown, but several causative factors have been considered including immunosuppression associated with CLL, ultraviolet (UV) light exposure, and the mutagenic effect of chemotherapy or radiotherapy. CLL is characterized by an impaired functioning of the immune system with dysfunctional lymphocytes unable to elicit an antitumor response.[11,75,76] Both exposure to UV radiation and immunosuppression are pivotal risk factors for the development of cSCC.[72,77] In our systematic review, elderly males are in a high-risk group, and cSCC are preferentially located on the head and neck region. These findings suggest the critical role of years of cumulative UV radiation exposure in the development of keratinocyte carcinomas, reinforcing the need of awareness and educational program of CLL patients on primary prevention strategies for skin cancer (e.g. sun avoidance, sun protection measures). Genetic susceptibility, environmental factor, and human papillomavirus infection have been reported to play a role in the oncogenesis of cSCC in CLL patients as well as in other immunosuppressed subsets of patients.[5,7,11]

Our review has some limitations. There is a high heterogeneity in the design, populations, and objectives of the included studies. Most of the included articles are case reports or case series involving a small number of patients. Moreover, we

included three studies based on data from the Swedish Cancer Registry[37,62,68] and five studies from the Mayo Clinic,[31,32,42,44,63] and we are not able to exclude that some duplicate cases were encompassed. As a result of the generally high risk of bias across the included studies, we could present only a narrative synthesis of the evidence, and it was not possible to perform a meta-analysis. The generally poor quality of the evidence base implies that caution is needed in the interpretation of our findings since there is significant uncertainty regarding the included data.

Our systematic review specifically examines the risk of cSCC in patients with CLL and provides a comprehensive picture of available epidemiological evidence on this topic. In addition, it confirms the relevant morbidity and mortality of cSCC in patients with CLL and strengthens the importance of prompt treatment and close dermatologic surveillance for this high-risk subset of patients. Future prospective studies with larger population are needed to increase the quality of evidence regarding the occurrence of cSCC in patients with CLL and to determine the best treatment modalities and screening intervals for these patients.

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