Competing risks analysis of Merkel cell carcinoma with concurrent chronic lymphocytic leukemia and non-Hodgkin lymphoma

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Abstract

Background: Although hematogenous malignancy is a risk factor for poorer prognosis in Merkel cell carcinoma (MCC), current guidelines make no specific recommendations for surveillance.

Objective: We aim to characterize MCC-specific mortality compared to other causes of death for patients with hematologic malignancy in MCC, which will guide workup and surveillance strategies.

Methods: The Surveillance, Epidemiology, and End Results-18 registry was queried for MCC patients with chronic lymphocytic leukemia (CLL) or non-Hodgkin lymphoma (NHL).

Results: Of 8519 patients with MCC, 146 (1.7%) had CLL and 234 (2.8%) had NHL. Chronic lymphocytic leukemia patients had 5-year cumulative incidence of MCC-specific mortality of 38.4% versus 28.4% in patients without CLL/NHL. For both cohorts, oncologic risk was highest within the first three years of diagnosis with competing risks favored thereafter. On competing risk regression, a history of CLL trended toward statistical significance with poorer MCC-specific mortality (subdistribution hazard ratio: 1.33, 95% CI: 0.963-1.834, P=0.084), while NHL was not prognostic.

Conclusions: Merkel cell carcinoma patients with CLL may benefit from more aggressive initial management. Surveillance for similar length in CLL patients with MCC may be appropriate; this co-morbidity did not affect the timeframe by which the risk of competing causes of death exceeded oncologic risks.

Keywords: hematogenous malignancy, Merkel cell carcinoma, surveillance

Introduction

Merkel cell carcinoma (MCC) is an aggressive, neuroendocrine tumor with a propensity for rapid progression and early dissemination with a low 5-year overall survival (OS) rate of 40% [1]. Systemic immunosuppression from hematologic malignancy, human immunodeficiency virus (HIV), or medication used to manage autoimmune diseases or organ transplant recipients, has been identified as a key risk factor for the development of MCC [2]. Lymphoproliferative disorders, such as chronic lymphocytic leukemia (CLL) or non-Hodgkin lymphoma (NHL) are significantly associated with incidence of MCC and in some cohorts, CLL has represented as much as a 30-fold overrepresentation in patients with MCC compared to the generalized population [3-5].

Immunosuppression status has demonstrated poorer MCC-specific survival in a stage-independent manner with a 3-year rate of 40% versus 74% compared to individuals who are not immunosuppressed in one investigation [3]. In a prior cancer registry study, a history of CLL was associated with worse cause-specific survival in both MCC and melanoma [4]. Immunosuppression constitutes a heterogenous group of individuals, and in one study, patients with hematogenous malignancies such as CLL had more favorable MCC-specific survival than those with HIV/AIDS [5].

Given the rarity of MCC, optimal workup, initial management, imaging, and surveillance strategies remain an ongoing investigation, particularly for patients with immunosuppression. Although current National Comprehensive Cancer Network (NCCN) guidelines recommend aggressive surveillance for the first three years of diagnosis, whether this should vary in the setting of comorbid hematogenous malignancies can be further investigated [6]. In this study, we aim to investigate how hematologic malignancy affects the clinical presentation and course of MCC, which may clarify how initial workup, imaging, and surveillance strategies may be further individualized in this setting and guide future research in this area. Thus, we performed an investigation in the Surveillance, Epidemiology, and End Results (SEER) cancer registry to examine clinical features of MCC patients with CLL/NHL and performed a competing risk analysis of patients with MCC and concurrent CLL/NHL to assess at what duration the probability of competing risks outweighs that of MCC-specific mortality.

Methods

Study design

Surveillance, Epidemiology, and End Results (SEER)-18, a population-based registry encompassing approximately 28% of cancer diagnoses within the United States, was queried for patients diagnosed with MCC from 2000 to 2017 [7]. *International Classification of Disease for Oncology-Third Edition* (ICD-O-3) morphology code 8247 was used to identify individuals with MCC. ICD-O-3 code 9823 was used to capture those with chronic/lymphocytic leukemia, whereas non-Hodgkin lymphoma codes encompassed 9590, 9591, 9596, 9670, 9671, 9673, 9680, 9789, 9690, 9691, 9695, 9698, 9699, 9700, 9701, 9702, 9705, and 9709.

Within the SEER registry, primary site of lesion (head and neck, trunk, upper/lower extremities), SEER disease stage (localized, regional, distant), age of diagnosis, sex, and duration of follow-up were evaluated. Patients with MCC and CLL/NHL were identified in parallel and then concurrent diagnoses were merged using internal SEER patient identifiers. A pre-existing diagnosis of either CLL or NHL was classified as a date of diagnosis preceding the date of MCC diagnosis. Cause of death was identified as attributable to MCC versus all other causes. SEER summary staging classifies localized disease as malignancy with limited spread beyond the organ of origination and a lack of penetration of the epithelial basement membrane, whereas regional disease was defined as direct extension into contiguous lymph nodes or contiguous spread to adjacent tissue. Surveillance, Epidemiology, and End Results categorizes distant disease as disseminated or metastatic beyond the primary organ.

Statistical analysis

ANOVA and chi square tests were utilized to assess differences in clinicopathologic characteristics by patient cohorts with or without a history of CLL or NHL. Kaplan-Meier estimates were created to evaluate overall survival (OS) and MCC-specific survival by cohort, whereas the log-rank test was used to evaluate for statistical differences in prognosis. Fine-Grey competing risk analysis was used to estimate the cumulative incidence of both MCC-specific mortality with respects to competing risks and the Grey test was used to evaluate differences in cumulative incidence.

Competing risk regression analysis was performed to generate subdistribution hazard ratios (SHR) to identify independent prognosticators of MCC-specific mortality. Statistical analysis was performed with JMP 15.0.0 statistical software (SAS Institute Inc., Cary, NC, USA) and the cmprsk, crr-addson, and crr packages (R version 4.0.2). Statistical significance was considered if alpha ≤0.05.

Results

Of the 8519 patients who fulfilled the inclusion criteria for our study, 146 (1.7%) had a history of CLL, 234 (2.8%) had a history of NHL, and 8139 (95.5%) did not have a history of CLL/NHL (**Table 1**). Patients who had a history of CLL and NHL were on average older than those without a history of CLL/NHL (mean age of diagnosis: 76.7 and 75.2 versus 74.4, P=0.02) and they included a higher proportion of males (71.9% and 68.8% versus 62.5%, P=0.0009). No statistically

Table 1. *Comparison of clinicopathologic characteristics by patients with or without a history of chronic lymphocytic leukemia/non-Hodgkin lymphoma.*

CLL/NHL status				
	CLL	**NHL**	**No CLL/NHL**	**P values**
N (%)	146 (1.7%)	234 (2.8%)	8139 (95.5%)	
Sex				
Female	41 (28.1%)	73 (31.2%)	3049 (37.5%)	<0.0001
Male	105 (71.9%)	161 (68.9%)	5090 (62.5%)	
Primary site				
Head and Neck	66 (45.2%)	105 (44.9%)	2392 (47.8%)	<0.0001
Trunk	20 (13.7%)	24 (10.3%)	843 (10.4%)	
Upper/Lower Extremity	60 (41.1%)	105 (44.9%)	3403 (41.8%)	
SEER Disease Stage				
Localized	78 (53.4%)	143 (61.1%)	4599 (56.5%)	
Regional	47 (32.2%)	52 (22.2%)	1973 (24.2%)	<0.0001
Distant	13 (8.9%)	23 (9.8%)	767 (9.4%)	
Unknown	8 (5.5%)	16 (6.8%)	800 (9.8%)	
Age at diagnosis				
Mean (SD)	76.7 (8.3)	75.2 (8.8)	74.4 (10.5)	<0.0001
Median (IQR)	79 (70-85)	76.5 (69-83)	77 (68-84)	

significant differences were observed in these cohorts in distributions of primary sites (P=0.638) or SEER disease stage (P=0.104).

On Kaplan-Meier analysis of OS, patients with a history of CLL or NHL demonstrated poorer survival outcomes than those without a history of CLL/NHL (5-year OS of 30.9% and 36.1% versus 42.7%, P<0.0001, log-rank test), (**Figure 1A**). On analysis of MCC-specific survival, patients with a history of CLL exhibited worse outcomes (5-year MCC-specific survival: 51.4%, P=0.0006, log-rank test), whereas no differences in MCC-specific survival were observed between patients with a history of NHL and without a history of CLL/NHL on pairwise comparison (5-year MCC-specific survival: 67.3% versus 66.7%, P=0.966), (**Figure 1B**).

The 5-year cumulative incidence for MCC-specific mortality and all other causes were examined by patient cohort (**Figure 2A**). Patients with a history of CLL had the highest 5-year cumulative incidence of MCC-specific mortality at 38.4%, whereas individuals with NHL and those without a history of CLL/NHL demonstrated 5-year incidences of 25.4% and 28.4%, respectively. By the end of three years of follow-up, at least 90% of all deaths attributed to MCC had occurred in patients with a history of CLL. Patients with a history of NHL had the highest 5-year cumulative incidence of mortality from all other causes at 38.5%, whereas this incidence was lower in patients with CLL and without a history of CLL/NHL at 30.7% and 28.9%, respectively. When comparing the conditional probabilities of failure for patients with a history of CLL versus those without a history of CLL/NHL, the risks of MCC mortality versus all other causes reached parity at approximately within the first two and a half years of follow-up (**Figure 2B**). Thereafter, other causes of mortality demonstrated a higher likelihood than MCC-specific mortality.

Fine-Grey competing risk regression analysis evaluated for independent prognosticators of MCC-specific mortality appear in **Table 2**. It was observed that increasing age (SHR: 1.02, 95% CI: 1.013-1.022, P<0.0001), male sex (SHR: 1.76, 95% CI: 1.29-1.56, P<0.0001), and distant (SHR: 6.31, 95% CI: 5.58-7.14 P<0.0001) and regional disease compared to localized disease were associated with poorer MCC-specific mortality. Notably, a history of CLL trended toward statistical significance with poorer outcomes (SHR: 1.33, 95% CI: 0.96-1.83, P=0.084).

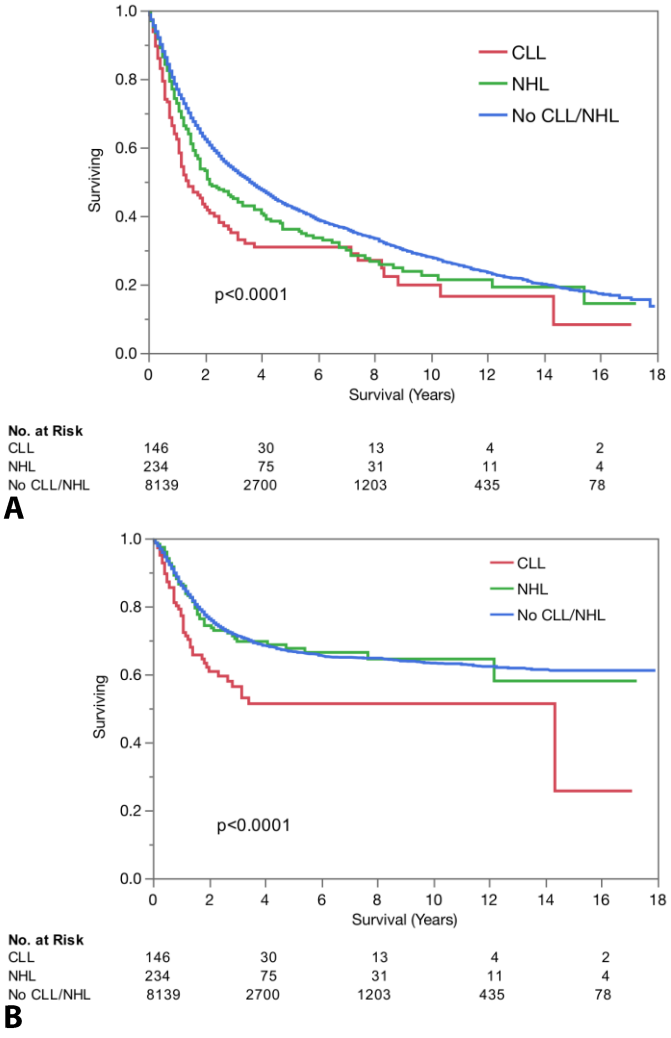

Figure 1. ***A)*** *Comparison of overall survival by history of chronic lymphocytic leukemia/non-Hodgkin lymphoma.* ***B)*** *Comparison of disease-specific survival by history of chronic lymphocytic leukemia/non-Hodgkin lymphoma.*

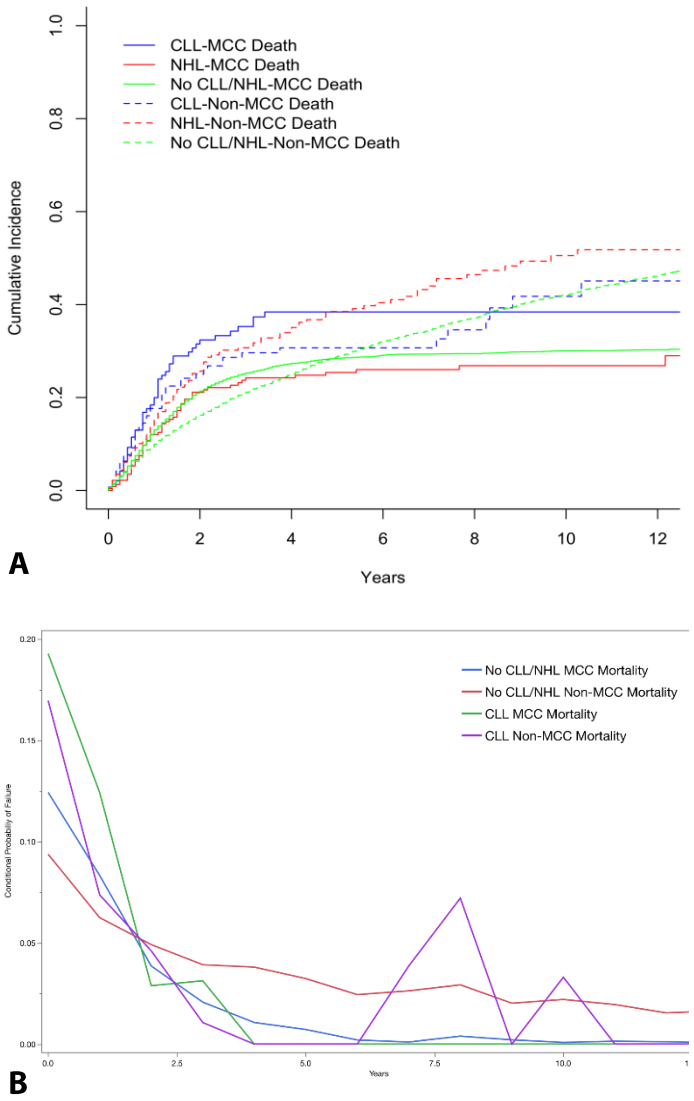

Figure 2. ***A)*** *Cumulative incidence of mortality of either Merkel cell carcinoma-specific death versus all other causes by history of chronic lymphocytic leukemia/non-Hodgkin lymphoma.* ***B)*** *Comparison of conditional probability of survival by history of chronic lymphocytic leukemia.*

Discussion

Immunosuppression is a significant risk factor predisposing to worse outcomes for patients with skin cancer [8-10]. Our investigation is consistent with a prior SEER study demonstrating that MCC patients with a history of CLL, but not other hematologic malignancies, had worse MCC-specific survival [4]. Although the authors in this previous study utilized standardized mortality ratios, our analysis encompassed a larger sample size, used a Fine-Grey analysis to produce an estimate of events in the setting of competing risks compared to Kaplan-Meier estimation. Our analysis controlled for more covariates, such as primary site or disease stage to better inform management strategies [11].

Current NCCN guidelines recommend careful follow-up every 3-6 months for the first three years of diagnosis followed by every 6 to 12 months given the high risk of locoregional recurrence and distant metastasis [6]. The recommended frequency of follow-up is flexible to allow clinicians to accommodate a personalized surveillance schedule based on individual risk factors. However, a paucity of evidence currently exists in the literature to guide the surveillance of MCC patients with a history of CLL/NHL. Our Fine-Grey analysis demonstrated that at least 90% of deaths attributed to MCC occurred within the first three years in patients with a history

Table 2. *Competing risk regression analysis for determinants of Merkel cell carcinoma-specific mortality.*

Variable	Subdistribution Hazard Ratio (SHR) (95% CI)	P value
Age at Diagnosis	1.02 (1.013-1.022)	<0.0001
Sex		<0.0001
Female	1.0	
Male	1.42 (1.29-1.56)	
Primary Site		
Upper/Lower Extremities	1.0	
Trunk	1.02 (0.88-1.17)	0.84
Head and Neck Other	0.89 (0.81-0.97)	0.011
SEER Disease Stage		
Localized	1.0	
Regional	2.53 (2.29-2.80)	<0.0001
Distant	6.31 (5.58-7.14)	<0.0001
Unknown	2.10 (1.82-2.42)	<0.0001
CLL/NHL Status		
No CLL/NHL	1.0	
CLL	1.33 (0.96-1.83)	0.084
NHL	0.92 (0.71-1.20)	0.55

of CLL, a trend that is also observed in patients without a history of CLL. Notably, our conditional probability of failure analysis demonstrated that the MCC-specific risks exceeded that of competing risks within the first two and half years for our cohort, regardless of a history of CLL/NHL. After this initial period, patients carried a higher non-oncologic risk of mortality. Thus, our data suggest that similar surveillance strategies currently recommended by the NCCN, focusing heavily on surveillance within the first three years of diagnosis, may also be applied in individuals with MCC who have a history of CLL/NHL.

Many advances have been made recently regarding workup and surveillance for MCC. For example, a recent investigation has suggested that there is high utility to baseline positron emission tomography/computed tomography (PET-CT) in early stage MCC patients [12]. This is reflected in recent amendments to NCCN guidelines. In conjunction with our findings, baseline PET-CT could be even further justified in the setting of co-morbid CLL, given the worse MCC-specific survival in this population. In addition, MCPyV oncoprotein antibody titers can be monitored in polyomavirus positive cases as an indicator for recurrent disease [13, 14]. As patients with CLL demonstrated a higher cumulative incidence of MCC-mortality than those without CLL/NHL, these patients could potentially benefit from more frequent follow-up with whole-body ^{18}F-fluorodeoxyglucose PET/CT or with MCPyV oncoprotein serology testing within the first three years of diagnosis. This approach would allow for more accurate prognostication. In the case that disseminated disease is discovered, this would allow for timely initiation of immune checkpoint blockade, which have demonstrated clinical efficacy in patients with hematogenous malignancies [15]. Some evidence in melanoma suggests that lower tumor burden correlates with better outcome from immune checkpoint inhibition [16]. If the same principle were true in MCC, personalized surveillance protocols could allow for more prompt recognition of disseminated disease and better outcomes for patients. In addition, for individuals with clinical N0 disease with adverse risk factors, adjuvant radiation is recommended after primary excision owing to the higher risk of locoregional recurrence. Our study further substantiates the relevance of CLL as a risk factor for greater MCC-specific mortality and serves as an additional piece of evidence to be considered when deciding to offer adjuvant radiation. Of patients with MCC, those with a history of CLL constituted a minority of the overall cohort (1.7%). On regression analysis, although a history of CLL trended toward statistical significance, this observation that can likely be strengthened with an increased patient cohort size. Collectively, our data suggest that aggressive monitoring should be performed within the first three years of diagnosis in accordance with current guidelines. However, patients with MCC often receive this diagnosis at an advanced age and have many co-morbidities. Given these considerations, surveillance and management should continue to be carried forth in a personalized manner in coordination with an oncologist.

Limitations of our study include its retrospective nature and lack of other pertinent clinical characteristics such as degree of comorbidities, polyomavirus status, lymphovascular invasion, recurrence, or progression-free survival.

Conclusion

Current clinical guidelines do not offer specific recommendations for patients with MCC who may have concurrent hematologic malignancies and who likely will demonstrate poorer prognosis owing to immunosuppression. Our analysis indicates that this subset of patients has the highest MCC-specific risk within the first three years of diagnosis, similarly to those without a history of CLL/NHL and could benefit from more aggressive initial workup, management, or surveillance during this period.

Potential conflicts of interest

The authors declare no conflicts of interest.

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