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SHORT REPORT

Impact of chronic lymphocytic leukaemia on melanoma outcomes: A retrospective case-control study

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Summary

With new, effective treatments for chronic lymphocytic leukaemia (CLL) the impact of second malignancies is increasingly important. We performed a retrospective case-controlled study examining the effect of CLL and its treatment on melanoma-specific survival and recurrence. A total of 56 patients with melanoma with CLL were matched 1:1 to patients without CLL for age, date of diagnosis, gender and melanoma tumour, node, metastasis (TNM) stage. Multivariate analysis found CLL was associated with significantly worse melanoma-specific mortality (hazard ratio [HR] 2.46, 95% confidence interval [CI] 1.27–4.74, $p = 0.007$) and recurrence (HR 3.44, 95% CI 1.79–6.63, $p < 0.001$). Patients with CLL had poor immunotherapy tolerance and prior CLL treatment was not associated with melanoma outcomes.

KEYWORDS
chronic lymphocytic leukaemia, melanoma, recurrence, survival, treatment

INTRODUCTION

Melanoma is a common potentially fatal malignancy and patients with chronic lymphocytic leukaemia (CLL) are at greater risk of developing melanoma and have worse melanoma-specific survival.[1-5] The impact of CLL on melanoma recurrence in high-stage melanoma is currently unknown.[6]

The treatment of CLL with immunosuppressive agents including chemotherapy and rituximab have been hypothesised to impact melanoma-specific survival (MSS) and recurrence-free survival (RFS) by impairing the anti-tumour response allowing other malignancies like melanoma to develop more readily and aggressively.[7-10] While there is some evidence to suggest CLL chemotherapy treatment is associated with increased melanoma incidence, there are no studies examining the impact on MSS or RFS.[7] Melanoma treatment can also be challenging in the CLL cohort, as patients with underlying lymphoproliferative disease are intrinsically more likely to develop autoimmune complications and it is currently unknown whether melanoma immunotherapy can exacerbate these adverse events.[11,12]

Recent advances in targeted therapies for patients with CLL have resulted in longer life expectancies and thus increasing their risk of developing and dying from second malignancies including melanoma.[13-15] The understanding and management of melanoma in this vulnerable group is therefore more important than ever. We investigated the association of CLL and its treatment on MSS and RFS in a retrospective case-control cohort study and explored immunotherapy adverse events.

PATIENTS AND METHODS

Study design

We performed a retrospective case-control study and matched patients with melanoma with a past history of CLL to patients without CLL 1:1 for age at melanoma diagnosis

±5 years, date of melanoma diagnosis ±10 years, gender and melanoma TNM stage. This study was approved by the institutional review boards of the two participating centres.

Data Collection and Statistical Analysis

Medical records were examined for demographic, pathology, treatment and survival data. Survival time was calculated as time between the date of melanoma histopathological diagnosis and date of death. Patients were censored by the last follow-up date or death from other causes. Recurrence was calculated as time between the date of primary melanoma and first recurrence and censored by the last recurrence-free follow-up date. Demographics, melanoma characteristics and type of melanoma recurrence were tested for differences between CLL and no CLL groups using *t*-test, chi-squared test or Fisher's exact test depending on whether the data were categorial, continuous or sparse. MSS and RFS were estimated by the Kaplan–Meier method and compared using log-rank (Mantel–Cox) test. The median follow-up time was calculated using the Schemper and Smith method.[16] Cumulative incidence functions were calculated using the Kalbfleisch and Prentice method[17] and groups were statistically compared using the Grey test.[18]

The Cox proportional-hazards regression method was used to assess the association of melanoma-specific mortality and recurrence. A parsimonious multivariate model was built using variables if they were both significant on univariate analysis and biologically plausible or known to be associated with melanoma survival/recurrence. Variables were tested for correlation using Spearman's test and correlated variables were excluded from multivariate analysis.

RESULTS

We matched 56 patients with melanoma and a past history of CLL to patients without CLL. There were no statistically significant differences in demographics, melanoma characteristics or melanoma treatment between groups (Table S1). The median difference in the date of melanoma diagnosis between the CLL and no CLL group was 24 days.

The median MSS was 50.2 months in the CLL group and not reached in the no CLL group due to insufficient events. The median RFS of the CLL group was 41.2 months and was not reached in the no CLL group. Five patients in both groups were excluded from RFS analysis as they had metastatic disease at initial presentation. Recurrence of melanoma occurred in 53% ($n = 27$) of patients with CLL compared to 27% ($n = 14$) in patients without CLL. Both MSS and RFS survival curves were significantly worse in the CLL group compared to the no CLL group ($p = 0.004$ and $p = 0.0002$ respectively, Figure 1). The CLL group had more locoregional melanoma recurrence compared to distant recurrence; however, this was not statistically significant ($p = 0.18$) (Table S2).

Uni- and multivariable analyses found melanoma stage was strongly associated with melanoma-specific mortality and recurrence (Table 1). An older date of melanoma diagnosis was associated with significantly poorer melanoma-specific mortality in univariate analysis ($p = 0.01$) and significance was nearly reached in multivariate analysis ($p = 0.06$). A past history of CLL was associated with significantly worse melanoma-specific mortality (hazard ratio [HR] 2.46, 95% confidence interval [CI] 1.27–4.74, $p = 0.007$) and recurrence (HR 3.44, 95% CI 1.79–6.63, $p < 0.001$) in both uni- and multivariate analysis.

A past history of CLL and prior CLL treatment were strongly correlated (Spearman's coefficient $r = 0.49$, $p < 0.01$) and hence only a past history of CLL was included in the multivariate model to avoid interactions. We found no significant association between the prior treatment of CLL (either with chemotherapy or chemotherapy and rituximab) and melanoma-specific mortality ($p = 0.74$) or recurrence ($p = 0.42$). A total of 23 patients with CLL had treatment with either chemotherapy plus rituximab (10 patients), chemotherapy (seven), Bruton tyrosine kinase inhibitor (four) or other treatments (six). All treated CLL patients received treatment prior to their melanoma diagnosis.

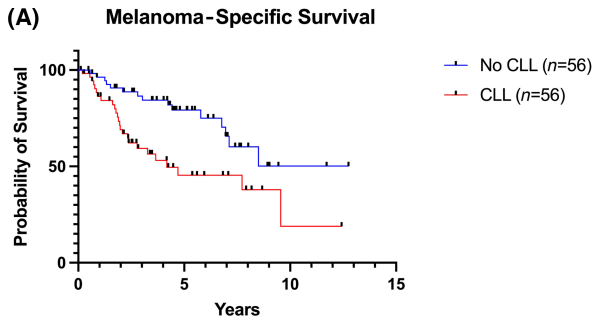
In all, 14 patients with CLL and 14 control patients received immunotherapy for the treatment of melanoma. Adverse events requiring cessation of immunotherapy occurred in 43% (six of 14) of patients with CLL compared to 7% (one of 14) of patients without CLL. Adverse events in the CLL group consisted of colitis/enteritis ($n = 3$), autoimmune haemolytic anaemia ($n = 2$) and pneumonitis ($n = 1$). One patient without CLL had recurrent bowel pseudo-obstructions secondary to immunotherapy.

DISCUSSION

We found that patients with melanoma and a past history of CLL had significantly worse melanoma-specific survival and recurrence compared to those without CLL. This is the first study to show worse melanoma recurrence in the CLL cohort and examine the association of CLL treatment with melanoma outcomes.

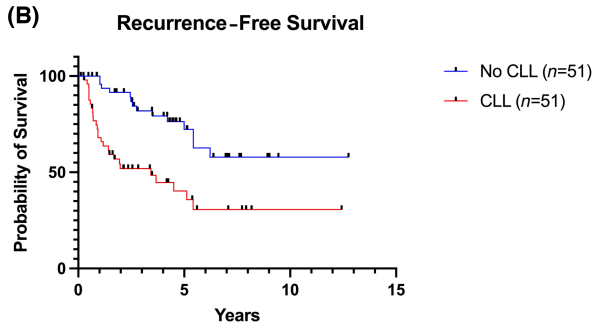
Cancer registry studies[4,5] have previously demonstrated that CLL is associated with worse melanoma-specific survival; however, only a single retrospective cohort study[5] has examined CLL and RFS. That study described 40 patients with CLL and found there was no association with CLL and RFS; however, the majority of patients had Stage 0 and 1 melanoma compared to our study that had higher stage melanoma at presentation and could explain the difference. One hypothesis to explain this high rate of melanoma recurrence could be the CLL lymphocyte's ability to alter the lymphatic microenvironment, which may decrease the anti-tumour response and allow neoplastic cells to proliferate and metastasise via lymphatics more readily.[19,20]

While the treatment of CLL has been associated with an increased risk of developing melanoma,[7] case studies have hypothesised that CLL treatments could worsen



Numbers at Risk

Year	0	1	2	3	4	5	6	7	8	9	10
No CLL	56	52	47	41	37	25	19	15	8	5	3
CLL	56	43	33	21	17	12	9	8	5	3	2



Numbers at Risk

Year	0	1	2	3	4	5	6	7	8	9	10
No CLL	51	48	42	33	30	19	14	11	5	3	2
CLL	51	33	22	17	13	10	6	6	3	2	2

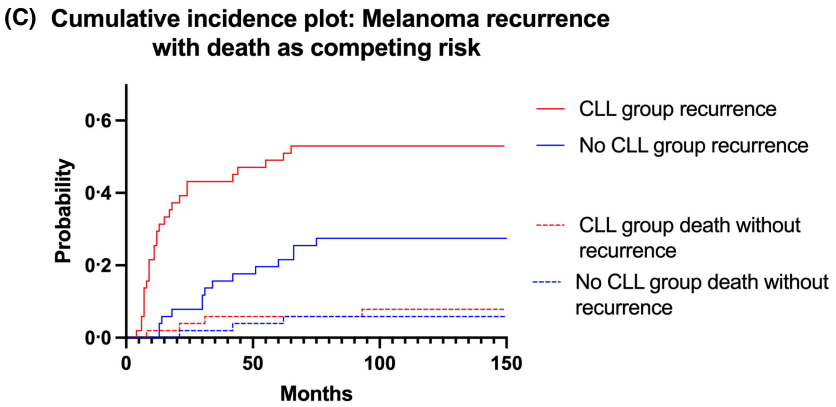


FIGURE 1 Kaplan–Meier survival curves of (A) melanoma-specific survival (MSS) and (B) recurrence-free survival (RFS) in patients with melanoma with CLL compared to no CLL. Log-rank comparison between CLL and no CLL groups for MSS and RFS were significantly worse in the CLL group ($p = 0.004$ and $p = 0.0002$ respectively). (C) Cumulative incidence plot of melanoma recurrence with death from non-melanoma related cause as competing risk in both CLL and no CLL groups. Grey's test found a statistically significant difference in melanoma recurrence between the CLL and no CLL group ($p = 0.0005$), but not for death from other causes ($p = 0.70$) [Colour figure can be viewed at wileyonlinelibrary.com]

immunosuppression and lead to poor melanoma outcomes.[9,10] Our Cox regression analysis did not find a significant association between the prior treatment of CLL and melanoma-specific mortality or recurrence. One hypothesis to explain this lack of association is the length of time between CLL chemotherapy administration and melanoma diagnosis. It is foreseeable that any induced lymphocyte depletion from CLL chemotherapy or rituximab and subsequent immunosuppressive affect would not impact melanoma diagnosed years later. In addition, CLL is immunosuppressive and therefore CLL treatment may improve the immune systems overall anti-tumour response, although we did not find any evidence of a positive association in our study.

Poorer tolerance to immunotherapy could also impact MSS and RFS in the CLL cohort. Tolerance is highly dependent on the immunotherapy medication with adverse events resulting in discontinuation occurring in approximately 9%–42% of patients in the general melanoma population.[21] The safety of immunotherapy in CLL has not been

TABLE 1 Uni- and multivariate melanoma-specific mortality and melanoma recurrence models

	Univariate analysis		Multivariate analysis	
Variable	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Melanoma-specific mortality				
Age at melanoma diagnosis (years)	1.00 (0.97–1.03)	0.79		
Date of melanoma diagnosis				
2000–2010	Ref.			
2011 onwards	0.43 (0.22–0.82)	0.01	0.54 (0.28–1.03)	0.06
Gender				
Male	Ref.	0.72		
Female	1.17 (0.49–2.80)			
Melanoma stage	2.90 (2.00–4.20)	<0.001	2.91 (2.01–4.20)	<0.001
Past history of CLL				
No	Ref.			
Yes	2.42 (1.26–4.63)	0.008	2.46 (1.27–4.74)	0.007
Melanoma location				
Other	Ref.			
Scalp/neck	1.49 (0.53–4.18)	0.45		
Melanoma subtype				
Superficial spreading	Ref.			
Nodular	1.63 (0.61–4.32)	0.33		
Lentigo maligna	1.27 (0.29–5.67)	0.75		
Other	2.28 (0.74–7.00)	0.15		
Prior CLL treatment				
No	Ref.			
Yes	0.87 (0.37–2.03)	0.74		
Prior CLL chemotherapy				
No	Ref.			
Yes	1.08 (0.44–2.61)	0.87		
Prior CLL chemotherapy and rituximab				
No	Ref.			
Yes	0.65 (0.19–2.23)	0.50		
Melanoma recurrence				
Age at melanoma diagnosis (years)	1.01 (0.98–1.05)	0.38		
Date of melanoma diagnosis				
2000–2010	Ref.			
2011 onwards	0.66 (0.33–1.29)	0.22		
Gender				
Male	Ref.			
Female	0.96 (0.42–2.16)	0.92		
Melanoma stage	2.72 (1.75–4.23)	<0.001	2.74 (1.79–4.20)	<0.001
Past history of CLL				
No	Ref.			
Yes	3.20 (1.67–6.13)	<0.001	3.44 (1.79–6.63)	<0.001
Melanoma location				
Other	1.49 (0.53–4.18)	0.45		
Scalp/Neck				

(Continues)

TABLE 1 (Continued)

	Univariate analysis		Multivariate analysis	
Variable	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Melanoma subtype	Ref.			
Superficial spreading	1.30 (0.57–2.94)	0.53		
Nodular	1.19 (0.35–4.00)	0.78		
Lentigo maligna	2.25 (0.85–6.01)	0.11		
Other				
Prior CLL treatment				
No	Ref.			
Yes	1.38 (0.64–2.98)	0.42		
Prior CLL chemotherapy				
No	Ref.			
Yes	1.49 (0.67–3.33)	0.33		
Prior CLL chemotherapy and rituximab				
No	Ref.			
Yes	0.48 (0.14–1.59)	0.23		

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukaemia; HR, hazard ratio.

thoroughly examined because patients with lymphoproliferative disease were excluded from immunotherapy clinical trials.[21-26] A small case series[12] found similarly high rates of melanoma immunotherapy intolerance in patients with CLL as our study (43%, six of 14). Given our small sample size, this potential association of CLL and poorer immunotherapy tolerance should be interpreted with caution. The mechanism is unclear; however, CLL lymphocytes overexpress immunotherapy targets including programmed death-ligand 1 (PD-1),[27] which may result in a brisker immunotherapy response. Alternatively, the generalised dysregulation of host immunity in patients with CLL may increase the risk of autoimmune disease.[28]

Our study design is limited by a small sample size, low event numbers as well as a long, heterogenous observation period. Melanoma survival times have significantly improved over time[29] due to advances in treatment and we have attempted to control for this by matching for date of diagnosis and incorporating melanoma date of diagnosis in our multivariate model. It is reassuring that melanoma treatment, specifically immunotherapy use, was similar between groups suggesting that disproportionate use of newer therapies did not confound survival results. Despite these limitations, the lack of current data in the literature means this study provides novel, valuable insights into the impact of CLL on melanoma outcomes.

With new and effective treatments, patients with CLL are living longer and the impact of second malignancies on their survival is becoming increasingly important. We found that the patients with CLL who developed melanoma had poorer MSS, RFS and potentially poorer immunotherapy intolerance. Patients with CLL with newly diagnosed melanoma should be counselled about this recurrence risk and possible immunotherapy complications. Future studies should investigate the most appropriate management in this vulnerable population.

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Dale Jobson designed the study, collected, interpreted, cleaned, checked and analysed the data, and wrote the manuscript. Christopher J. McCormack, Constantine Tam, Michael A. Henderson designed and supervised the study as well as supervised the interpretation and analysis of the data and reviewed and approved the final version of the manuscript. Victoria Mar supervised the collection of data and reviewed and approved the final version of the manuscript. Dale Jobson completed this research work as part of a Master of Science with the University of Edinburgh. Constantine Tam is supported by the CLL Global Foundation. Open access publishing facilitated by The University of Melbourne, as part of the Wiley - The University of Melbourne agreement via the Council of Australian University Librarians. [Correction added on 26 May 2022, after first online publication: CAUL funding statement has been added.]

CONFLICT OF INTEREST

Constantine Tam has an honorarium and research funding from Janssen, Abbvie and Beigene. Victoria Mar has received honoraria from Merck, Novartis and Bristol-Myers-Squib and research funding from MoleMap.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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