SHORT COMMUNICATION

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Increased risk of second malignancies in chronic lymphocytic leukaemia patients as compared with follicular lymphoma patients: a Canadian population-based study

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Background: Chronic lymphocytic leukaemia (CLL) patients have an increased risk of other malignancies. This may be due to surveillance bias, treatment or immunosuppression.

Methods: Cohort study of 612 consecutively diagnosed CLL patients in a Canadian province, with comparisons to follicular lymphoma (FL) patients.

Results: Treated CLL patients had a 1.7-fold increased risk of second cancers compared with untreated CLL patients. As compared with untreated FL patients, untreated CLL patients had a two-fold increased incidence of second malignancies.

Conclusion: Chronic lymphocytic leukaemia patients have an inherent predisposition to second cancers and the incidence is further increased by treatment.

Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) is the most common leukaemia in adults (Johnston *et al*, 2009). Primary causes of death consist of second cancers, progressive disease and infections (Wierda *et al*, 2009; Yoon *et al*, 2012). Patients with CLL/SLL have an impaired immune system, and this may partly explain the increased incidence of second malignancies (Molica, 2005). However, the increased incidence of second cancers may also be related to an inherent predisposition to malignancy, to the effects of systemic therapy or to surveillance bias due to close lifetime monitoring.

A retrospective population study in Manitoba, Canada, 40 years ago showed that the risk of all cancers was increased three-fold in CLL, while the increase in skin cancers was eight-fold (Manusow and Weinerman, 1975). Subsequent studies have shown the same pattern (Tsimberidou *et al*, 2009; Royle *et al*, 2011b). In these studies, immunophenotyping for CLL/SLL diagnosis was not utilised. Therefore, at least 10% of patients may have been misclassified (Seftel *et al*, 2009). Second, most Cancer Registries do not capture non-melanoma skin cancers (NMSCs), the major contributor to the incidence of second cancers in CLL/SLL patients.

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Furthermore, a cancer-free control population is commonly utilised that may lead to inaccuracy, as one cancer diagnosis increases the risk of development and detection of subsequent malignancies (Nugent *et al*, 2005; Morton *et al*, 2010; Royle *et al*, 2011b).

In the current study, we used Cancer Registry and immunophenotypic data in order to create a population-based cohort of confirmed CLL/SLL patients. Importantly, this cancer registry routinely captures NMSCs, as NMSCs are reportable in Manitoba. We compared CLL/SLL patients to the general population of Manitoba as well as to patients with follicular lymphoma (FL), another indolent B-cell malignancy with prognosis and long-term clinical surveillance similar to CLL/SLL. Furthermore, in Manitoba, FL patients received similar chemotherapy regimens to CLL/SLL patients (Chlorambucil and Fludarabine) for the majority of this study period. Comparison with a similar cancer cohort significantly reduces biases (e.g., surveillance and treatment bias) that could be introduced by comparing a cancer cohort with the cancer-free population. We also evaluated the impact of systemic therapy on the incidence of second cancers. Finally, we examined malignancies in CLL/SLL patients both before and after the diagnosis of CLL/SLL.

METHODS

The CLL/SLL cohort (subsequently referred to as CLL) has been previously published (Seftel *et al*, 2009). All immunophenotypically confirmed CLL and FL diagnoses in Manitoba between January 1998 and December 2003 were obtained from the Manitoba Cancer Registry. In accordance with the previous study (Seftel *et al*, 2009), NCI-WG 1996 diagnosis criteria (Cheson *et al*, 1996) were used. Ethics approval was obtained from the University of Manitoba Health Research Ethics Board.

We used a retrospective cohort design. Standardised incidence ratios (SIRs) were calculated as the ratio of observed number of second cancers in CLL patients to an expected number derived from age- and gender-standardised incidence of first cancers in the general population or second malignancies in FL patients. Person-years at risk was calculated for each person in the CLL or FL cohort from the date of diagnosis of CLL or FL, up to the date of diagnosis of the second cancer, date of death or 31 December 2009, whichever came first. Person-years at risk for Manitoba population was estimated by the sum of the Manitoba population for each year of the study (1998–2009). Three patients (0.6%) were diagnosed with a second cancer within 30 days of their CLL diagnosis and they remained in the study. Patients with a history of previous cancer and patients diagnosed with CLL at the time of death ($n = 11$) were excluded from SIR calculations. Sub-distribution hazard ratios were calculated using a competing risk regression model considering age and gender as covariates and death before a second cancer a competing risk (Fine and Gray, 1999). For purposes of the analysis, if patients were initiated on systemic treatment less than 6 months prior to the diagnosis of a second cancer they were considered untreated. Odds ratios (ORs) for history of previous cancers were estimated using a logistic regression model, adjusting for age, gender and year of diagnosis. Prevalence of previous cancers in the CLL cohort was compared with the prevalence of first cancers in the Manitoba population for the same age, gender and calendar year groups.

Data management and analysis were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA) and Stata 11.2 (Stata Corp., College Station, TX, USA).

RESULTS

Between 1998 and 2003, 612 CLL and 372 FL patients were diagnosed in Manitoba. For CLL and FL cohorts, median age at diagnosis was 71 (31–101) years and 63 (24–92) years, male-to-female ratios were 1.3 : 1 and 1.2 : 1, median follow-up was 6.4 (0–12) years and 6.9 (0–12) years, and median time to development of a second cancer was 3.3 (0–11.4) and 4.0 (0–11.3) years, respectively (Supplementary Table S1).

Chronic lymphocytic leukaemia patients had a 1.8-fold increase in the relative risk of a second cancer (SIR 1.79, 95% CI 1.30–2.45) compared with age- and gender-standardised FL patients. This increased risk was evident for all ages and both genders. The risk of NMSCs alone was more than two-fold higher in CLL patients compared with FL patients (SIR 2.27, 95% CI 1.38–3.74) and when stratified by gender this was only significant in males (SIR 3.12, 95% CI 1.60–6.10). Chronic lymphocytic leukaemia patients also

Table 1. Increased rates of second malignancies in patients with CLL as compared with FL patients and the general population of Manitoba

	CLL population			Compared with FL		Compared with GP	
Groups	***n***	**Time at risk (PY)**	**Second cancers**	**SIR**	**95% CI**	**SIR**	**95% CI**
All cancers							
All	255	2707.18	104	1.79[a]	1.30–2.45	1.93[a]	1.40–2.68
Male	260	1456.39	65	1.84[a]	1.23–2.75	2.05[a]	1.35–3.12
Female	195	1250.70	39	1.71[a]	1.02–2.84	1.76[a]	1.05–2.96
Invasive cancers (excluding NMSCs)							
All	499	3033.02	76	1.51[a]	1.06–2.14	1.62[a]	1.13–2.32
Male	288	1662.09	45	1.19	0.77–1.82	1.59[a]	1.00–2.53
Female	211	1370.93	31	2.49[a]	1.29–4.78	1.66	0.94–2.93
NMSCs							
All	538	3268.53	50	2.27[a]	1.38–3.74	40.42[a]	5.28–309.32
Male	299	1712.79	35	3.12[a]	1.60–6.10	38.57[a]	3.65–408.04
Female	239	1555.73	15	1.39	0.64–3.03	44.00	0.84–2304.23

Abbreviations: CI = confidence interval; CLL = chronic lymphocytic leukaemia; FL = follicular lymphoma; GP = general population; *n* = number of CLL cases; NMSCs = non-melanoma skin cancers; PY = Person-Years; SIR = standardised incidence ratio.
[a]Indicates statistical significance.

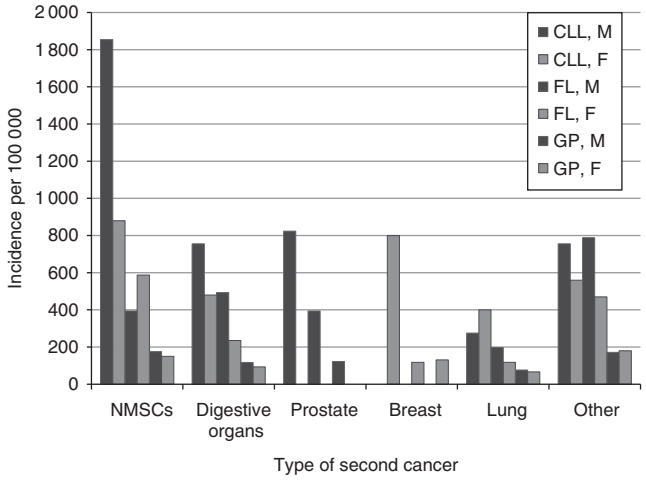

Figure 1. Site-specific incidence rates of second malignancies in CLL patients as compared with FL patients and the general population of Manitoba, by gender. Unadjusted incidence rates are calculated from 1998 to 2009 and are expressed per 100 000 persons. CLL = chronic lymphocytic leukaemia; F = female; FL = follicular lymphoma; GP = general population; M = male.

showed an increased risk of second cancers when compared with the general population of Manitoba (SIR 1.93, 95% CI 1.40–2.68; Table 1, Supplementary Tables S2 and S3).

The most common second cancer among CLL patients was NMSCs (37%), followed by cancers of digestive organs (16%), prostate (12%), breast (10%) and lung (9%). Second cancers in FL and the general population followed the same general pattern (Figure 1, Supplementary Tables S4–S6).

Both treated CLL and FL patients had an increased risk of second cancers compared with untreated CLL and FL patients, respectively. Untreated CLL patients had a two-fold increased incidence of second malignancies compared with untreated FL patients (Table 2, Supplementary Figures S1 and S2).

When previous cancers were investigated, patients with previous cancers showed a higher chance of developing CLL (OR 1.43, 95% CI 1.03–1.97, $P = 0.0322$). However when adjusted for age, the association disappeared (OR 0.99, 95% CI 0.70–1.41, $P = 0.9712$; OR age 1.58, 95% CI 1.42–1.76, $P < 0.0001$). Gender and year of diagnosis did not significantly improve the model. In addition, no significant difference in prevalence of previous cancers was observed between the CLL patients at the time of CLL diagnosis and the general Manitoba population of the same age and gender (data not shown).

DISCUSSION

In this population-based cohort study, patients with CLL had an almost two-fold increased incidence of second malignancies compared with patients with FL. Non-melanoma skin cancers were the most common second malignancy (37%), with a 2.3-fold increased risk in CLL compared with FL. When stratified by gender, this risk was only significant in male patients, and may be explained by the fact that men are more likely to work outdoors and receive greater exposure to UV radiation (Chen *et al*, 2013). The elevated incidence of NMSCs is consistent with previous reports, where skin cancers constituted 29.9% of all second cancers (Tsimberidou *et al*, 2009) and patients with CLL had a 3.66-fold increased risk of NMSCs when compared with the general population (Schöllkopf *et al*, 2007).

Table 2. Increased rates of second cancers in treated CLL and FL patients, and in untreated CLL patients compared with untreated FL patients

	CLL	FL
Treated (%)	141 (30)	202 (66)
Median TTFT (range)	5.3 mth (0–9.6 yr)	1.4 mth (0–9.0 yr)
Second cancer after treatment (%)	32 (23)	25 (12)
Median time from treatment to second cancer diagnosis (range)	3.1 yr (6.4 mth–11.2 yr)	4.0 yr (6.3 mth–11.2 yr)
Treated *vs* untreated SHR (95% CI)	Tx 1.81 (1.18–2.78) Age 3.80 (1.57–9.18)	Tx 2.47 (1.05–5.80) Age 2.52 (1.08–5.85)
Untreated CLL *vs* untreated FL SIR (95% CI)	2.05 (1.38–3.05)	

Abbreviations: CI = confidence interval; CLL = chronic lymphocytic leukaemia; Dx = diagnosis; FL = follicular lymphoma; mth = month; SHR = sub-Hazard ratio; SIR = standardised incidence ratio; TTFT = time to first treatment; Tx = treatment; Yr = year.

The increased incidence of second malignancies in CLL has been partly attributed to the profound immune deficiency seen in this disease (Tsai *et al*, 2009). An increased incidence of NMSCs has been closely related to immunosuppression after renal transplantation and other immunosuppressed individuals (Greene *et al*, 1978; García *et al*, 2013). Other studies have documented a high incidence of skin cancers in CLL patients and have noted a more aggressive disease course and increased mortality when compared with patients without CLL (Royle *et al*, 2011a). In our CLL cohort, deeper and longer degrees of immunosuppression might explain the high incidence of skin cancers in these patients as compared with the FL patients. Furthermore, it has been shown that patients with breast and colorectal cancers and a pre-existent CLL have an inferior overall and cancer-specific survival. This is suggested to be due to a less-effective immune response in CLL patients that consequently provides a more permissive environment for metastases (Solomon *et al*, 2013).

Chemotherapy can increase the incidence of second malignancies in CLL patients (Molica, 2005). In our study, the treated CLL and FL patients had substantially increased rates of second malignancies compared with untreated CLL and FL patients, respectively. However, it is important to highlight the two-fold higher incidence in untreated CLL patients compared with untreated FL patients, suggesting that treatment is not the sole contributor to the elevated risk of second cancers observed in CLL patients.

We have previously observed an increased incidence of non-Hodgkin lymphoma, melanoma, lung, prostate and breast cancers following a diagnosis of NMSC (Nugent *et al*, 2005). This suggests a common factor in the aetiology of these malignancies. In addition, an increased incidence of CLL has been observed in families of patients with colon cancer (Teruya-Feldstein *et al*, 2002) and an increased incidence of breast cancer has been noted in first-degree relatives of CLL patients (Linet *et al*, 1989). However, the role of genetic factors for secondary cancers in CLL patients is mitigated by our observation that the incidence of other malignancies is increased only after the diagnosis of CLL, rather than beforehand. Finally, the increased rates of second cancers in CLL patients cannot be attributed to treatment or surveillance bias, as in Manitoba FL patients undergo routine follow-up in a similar fashion to CLL patients.

It should be noted that CLL patients were diagnosed using the diagnostic criteria from 1996, which required patients to have a peripheral blood lymphocyte count of $> 5 \times 10^9$ per liter (Cheson *et al*, 1996). The updated definition from 2008 requires a

peripheral blood B-cell count of $>5\times10^9$ per liter (Hallek *et al*, 2008). Thus, a small proportion of our patients may have had monoclonal B-cell lymphocytosis. Second, patients diagnosed between 1998 and 2003 would have received treatment with single-agent chemotherapy. It remains to be seen if the second cancer rate will increase in patients receiving chemoimmunotherapy. Finally, our relatively small cohort and short follow-up yielded few second malignancies.

In conclusion, we have observed that the risk of second cancers in CLL patients is not only greater than the general population, but is also greater than a closely related lymphoproliferative disorder, FL. This increased risk is independent of treatment or surveillance bias. Of the second malignancies, skin cancers were the most common type. Heightened awareness about risks of second cancers should be communicated to improve the care and outcome of CLL patients.

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CONFLICT OF INTEREST

James Johnston is on the advisory board of Roche and received research funding from Roche Pharmaceuticals. Rajat Kumar is on the advisory board of Celgene. Other authors have no disclaimers.

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