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Original Research

Secondary malignancies among mantle cell lymphoma patients

Kossi D. Abalo [a,b,*], Karin E. Smedby [b,c], Sara Ekberg [b], Sandra Eloranta [b], Simon Pahnke [a], Alexandra Albertsson-Lindblad [d], Mats Jerkeman [d], Ingrid Glimelius [a,b]

[a] Department of Immunology, Genetics and Pathology, Cancer Precision Medicine, Uppsala University, Sweden
[b] Department of Medicine Solna, Clinical Epidemiology Division, Karolinska Institutet, Stockholm, Sweden
[c] Department of Hematology, Karolinska University Hospital, Stockholm, Sweden
[d] Division of Oncology, Department of Clinical Sciences Lund, Skåne University Hospital, Lund University, Lund, Sweden

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ABSTRACT

Purpose: With modern treatments, mantle cell lymphoma (MCL) patients more frequently experience long-lasting remission resulting in a growing population of long-term survivors. Follow-up care includes identification and management of treatment-related late-effects, such as secondary malignancies (SM). We conducted a population-based study to describe the burden of SM in MCL patients.

Methods: All patients with a primary diagnosis of MCL, aged ≥ 18 years and diagnosed between 2000 and 2017 in Sweden were included along with up to 10 individually matched population comparators. Follow-up was from twelve months after diagnosis/matching until death, emigration, or December 2019, whichever occurred first. Rates of SM among patients and comparators were estimated using the Anderson-Gill method (accounting for repeated events) and presented as hazard ratios (HR) with 95% confidence intervals (CI) adjusted for age at diagnosis, calendar year, sex, and the number of previous events.

Results: Overall, 1 452 patients and 13 992 comparators were followed for 6.6 years on average. Among patients, 230 (16%) developed at least one SM, and 264 SM were observed. Relative to comparators, patients had a higher rate of SM, HR_{adj}= 1.6 (95%CI:1.4–1.8), and higher rates were observed across all primary treatment groups: the Nordic-MCL2 protocol, R-CHOP, R-bendamustine, ibrutinib, lenalidomide, and R-CHOP/Cytarabine. Compared to Nordic-MCL2, treatment with R-bendamustine was independently associated with an increased risk of SM, HR_{adj}= 2.0 (95%CI:1.3–3.2). Risk groups among patients were those with a higher age at diagnosis ($p < 0.001$), males ($p = 0.006$), and having a family history of lymphoma ($p = 0.009$). Patients had preferably higher risk of melanoma, other neoplasms of the skin and other hematopoietic and lymphoid malignancies.

Conclusions: MCL survivors have an increased risk of SM, particularly if treated with R-bendamustine. The intensive treatments needed for long-term remissions are a concern, and transition to treatment protocols with sustained efficacy but with a lower risk of SM is needed.

1. Introduction

Mantle cell lymphoma (MCL) is an incurable mature B-cell neoplasm. With improving treatment concepts, MCL patients may experience long-lasting remission, both after the first and following lines of treatment, resulting in an increasing number of survivors with increasing demands for continuous good health and quality of life.

In younger MCL patients, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) alternating with R-cytarabine and consolidation with high-dose chemotherapy with autologous stem cell transplant (ASCT) has long been the standard treatment in the Nordic countries (the Nordic MCL2 protocol) [1]. These intensive treatments entail exposing patients to high doses of alkylating agents and substantially increasing the risk for long-term complications, particularly secondary malignancies (SM). The newly presented TRIANGLE study has shown a better prognosis with the addition of ibrutinib, a tyrosine kinase inhibitor, both during induction and as maintenance, even when removing the transplant [2], but is still based on intensive chemotherapy. In elderly patients, several immunochemotherapy combinations are still used, including R-CHOP and R-bendamustine [3,4]. Given that many of these agents, including bendamustine, induce dose dependent DNA damage [5,6], the risk of SM is important to consider.

* Correspondence to: Department of Immunology, Genetics and Pathology, Cancer Precision Medicine, Uppsala University, Uppsala, Sweden.
E-mail address: kossi.dovene.abalo@ki.se (K.D. Abalo).

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Novel targeted drugs are now being introduced in first-line treatment [7,8]. Ibrutinib has shown promising efficacy in relapsed MCL patients [4], and adding ibrutinib to R-bendamustine [9] and lenalidomide to rituximab during maintenance [10] have both shown improved outcomes in first-line [9,10]. However, it is uncertain if the transition to novel targeted drugs will reduce risks of SM. The improvements in prognosis have also resulted in a need to optimize survivorship care. The survival probability after 25 years of follow-up, for mature B-cell neoplasm patients with SM, was only 20% of that in patients without SM [11].

Only a few studies have addressed the burden of SM in MCL patients, and indicate that this population is at high risk [12–14]. The major limitations of prior studies are the small sample size and the lack of investigation of clinical and treatment related risk factors. Finally, previous studies on the risk of SM in MCL patients have rarely included comparisons with expected rates in the general population [12–14]. Therefore, we aimed to investigate the occurrence of SM in MCL patients treated with the Nordic MCL2 regimen, R-CHOP, R-bendamustine, radiotherapy and novel targeted drugs, using a large cohort of lymphoma patients.

2. Material and method

2.1. Participants

We identified all patients with a diagnosis of MCL aged $\geq$ 18 years at diagnosis from 2000 through 2017 who were registered in the Swedish Cancer Register (SCR) and in the Swedish Lymphoma Register (SLR). In Sweden, reporting to the SCR is mandatory by law since 1958 with almost complete coverage (~96.1%) for all non-Hodgkin lymphomas (NHL) combined [15]. The SLR is a nationwide quality-of-care register with a coverage of ~95% compared with the SCR [16,17]. The MCL data from year 2007 in the SLR were updated and completed through a nationwide medical record review. Data on clinical characteristics at diagnosis (age, sex, performance status, Ann Arbor stage, prognostic factors needed for the calculation of the MCL International Prognostic Index (MIPI): age at diagnosis, white blood cell count, lactate dehydrogenase level, and Eastern Cooperative Oncology Group (ECOG) performance status [18]), and data on first-line treatments for each patient were gathered from the SLR.

Up to ten general population comparators per patient were selected without replacement from the Register of the Total Population. The comparators were matched on birth year, sex, calendar year of diagnosis, were alive and were lymphoma-free at the diagnosis date of the corresponding patient.

The cohort (patients and comparators) was further linked to the Swedish Patient Register which has a nationwide coverage of hospitalizations since 1987 and specialist outpatient visits since 2001, and with the SCR to extract comorbid diseases, including cancer, within 10 years prior to MCL diagnosis (or matching). Comorbidities were classified according to the Charlson Comorbidity Index (CCI) [19]. Information on highest achieved educational level, civil status, and emigrations were obtained from the national database Longitudinal Integrated Database for Health Insurance and Labour Market Studies and the Population Register, respectively. The Swedish Cause of Death Register was used to retrieve the dates of death for all individuals. The final study population is outlined in Fig. S1.

2.2. Follow-up and outcome

For the majority of non-indolent MCL patients, first-line treatments are ongoing for approximately six to twelve months after diagnosis. However, certain patient groups may also receive their primary treatment later. We stipulated that malignancies that occurred during the treatment period of twelve months were less likely to be related to the MCL treatment. Consequently, we performed a left truncated analysis where follow-up started at 12 months after diagnosis thereby excluding patients who experienced the event or died during the first year after the initial diagnosis.

Any newly diagnosed malignancy occurring during follow-up was identified through a linkage with the SCR using the International Classification of Disease–10th version (ICD-10) codes. The first recorded malignancy within each ICD-10 code group by anatomical site (topography) during follow-up was considered an event for patients and comparators (denoted SM). All recurrent records of the same anatomical cancer site (e.g., repeated records of skin or colon cancers) were disregarded, but subsequent malignancies of other types (ICD-10 code groups) were considered as new events. We further retrieved information on family history of lymphoma through linkage to the Multigeneration Register and the SCR. For all neoplasms of uncertain or unknown behaviour (ICD10: D37-D48) and all malignant neoplasms stated or presumed to be of lymphoid, hematopoietic, and related tissue (ICD10: C81-C96), the register records were independently reviewed by an oncologist (IG) to ascertain potential misclassification since these chapters could potentially hide relapse or secondary MCL diagnoses. In this process four suspected relapses of MCL were identified and were subsequently excluded.

2.3. Statistical analysis

Socio-demographic and clinical characteristics were summarized and compared using chi-square tests. The follow-up started twelve months after primary diagnosis (matching date for comparators) and continued until death, emigration, or 31 December 2019, whichever came first. All new malignancies that occurred during follow-up were considered, thus implying that an individual remained at risk of new events even after the first SM. The event rate was estimated and presented as hazard ratios (HRs), contrasting patients to comparators, with 95% confidence intervals (CI) using the Andersen–Gill method [20]. This model is an extension of the Cox proportional hazards model and HRs are interpreted in a similar way [21,22]. The confidence intervals were estimated using a robust variance estimator proposed by Lin and Wei [23].

All models included a binary variable reflecting the exposure (patients versus comparators) status and the matching variables sex, age at diagnosis ($<$60, 60–69, 70–79, and $\geq$80 years), calendar year of diagnosis (2000–2004, 2005–2009, 2010–2014, and 2015–2017) and a time-dependent variable representing the order of events in individuals with more than one event occurring during follow-up. The models were parameterized to directly estimate the effect of the exposure in each stratum of the given variables. Interactions between the exposure status and the variables used for adjustment were formally tested using the Wald test [24].

Associations between clinical characteristics and the rate of SM were investigated in analyses restricted to the MCL patients whilst similarly adjusted for sex, age, calendar year of diagnosis, and the number of previous events.

The proportional hazards assumption was assessed using the Grambsch-Therneau test on the scaled Schoenfeld residuals.

The Kaplan-Meier method was used to estimate the net probability of the first SM (presented as 1 minus the Kaplan-Meier) among patients and comparators. To assess the real world probability, the cumulative incidence of contracting a first SM was estimated non-parametrically, incorporating death due to any causes as a competing event [25,26].

We also performed sensitivity analyses where follow-up started at 6, 18 and 24 months after diagnosis in order to assess the potential influence of surveillance bias on our results.

Stata version 15 (StataCorp. 2017, Stata Statistical Software: Release 15; College Station, TX: StataCorp LLC.) was used for data preprocessing and all statistical analyses were performed using R software [27].

2.4. Ethics

The study has been approved by the Regional Board of the Ethical Committee in Stockholm (2018/2631–31/2019–00242) and the ethical committee in Lund (Dnr 2012/212), Sweden.

3. Results

Overall, 15 444 participants were included (1 452 patients and 13 992 comparators). The median age at MCL diagnosis was 70 years (range 22–96 years). The cohort was followed up for 6.6 years on average (median 5.6 years, range 0–19 years). Seventy-three percent (73%) of the patients were male. Patients presented more frequently with a history of cancer (any type excluding MCL) ($p < 0.01$) and had more comorbidities ($p < 0.01$) than comparators (Table 1) at baseline.

During follow-up, a total of 264 SM were observed in 230 patients, representing 16% of all patients. Among patients with SM, 88% were diagnosed with only one SM (Fig. S2). The median age at the first SM diagnosis was 75.6 years (range 51.3–91.9 years).

3.1. Risk of secondary malignancies

The five-year overall net cumulative probability of SM was higher in patients (17.6%, 95%CI: 14.9%−20.2%), than in comparators (11.8%, 95%CI: 11.2%−12.4%) (Figure 1).

Over time MCL patients had 60% higher rate of SM than comparators, HR_{adj}= 1.6 (95% CI: 1.4–1.8). Higher rates in patients were seen in all age groups, both sexes, in each calendar period, and by all investigated demographic and clinical characteristics (Table 2). Further, when contrasted to comparators, higher rates were observed in patients irrespective of first line treatments: Nordic-MCL2 HR_{adj}= 1.4 (95% CI: 1.0–1.9), R-CHOP HR_{adj}= 1.8 (95% CI: 1.3–2.5), R-bendamustine HR_{adj}= 2.1 (95% CI: 1.7–2.7), lenalidomide HR_{adj}= 4.3 (95% CI: 2.0–9.0), R-CHOP/Cytarabine HRadj= 1.8 (95% CI: 1.2–2.6), and ibrutinib HR_{adj}= 4.8 (95% CI: 1.2–18.7), (Figure 2), and not significant for Fludarabine Cyclophosphamide (FC) and cytarabine (Fig. S3).

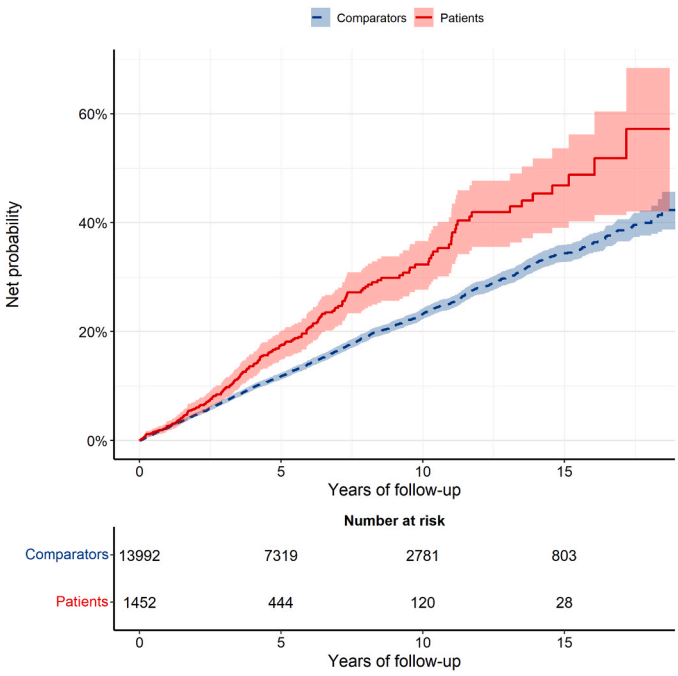

Fig. 1. Net probability (1-Kaplan Meier) of malignancies occurring in mantle cell lymphoma (MCL) patients and matched population comparators, twelve months from the diagnosis (matching) date. Individuals were censored at death.

When restricting the analyses to the MCL patients only, higher rates of SM were observed with increasing age at diagnosis ($p < 0.001$), in recent calendar years ($p = 0.012$), for males ($p = 0.006$), and for patients with a family history of lymphoma ($p = 0.009$) (Table 3). There was no evidence of differences in rates by stage (Ann Arbor) or MIPI. Compared to Nordic-MCL2, treatment with R-bendamustine was associated with an increased rate of SM, HRadj= 2.0 (95% CI: 1.3–3.2). Higher rates were also observed in the few patients treated with ibrutinib in first-line (n = 9 with ≤3 malignancies in ≤3 patients) HR_{adj}= 4.2 (95%CI: 1.7–10.9) and lenalidomide in first-line (n = 16, with 9 malignancies in 8 patients) HR_{adj}= 2.3 (95% CI: 1.3–4.2) (Table 4).

Fewer patients than comparators remained alive, and hence at risk of developing SM during follow-up. Accounting for the competing risk of death, the five-year cumulative incidence was 12.4% (95% CI: 10.5%−14.2%) for the patients and 10.9% (95% CI:10.4%−11.5%) for the comparators, respectively (Figure 3, Table S1).

Melanoma and other skin cancers (n = 109, 41%), male genital organ neoplasms (n = 38, 14%), neoplasms of digestive organs (n = 38, 14%), respiratory and intrathoracic organs (n = 18, 7%), urinary tract (n = 17, 6%) and lympho-hematopoietic malignancies (excluding MCL, n = 17, 6%, Table S3) were the most frequently occurring SM. Relative to comparators, higher rates of SM of uncertain or unknown behavior (n = 9, 3%) HR_{adj}= 5.0 (95% CI: 2.4–10.5), melanoma and other malignant neoplasms of skin HR_{adj}= 2.9 (95% CI: 2.4–3.5), and hematopoietic malignancies (excluding MCL, Table S3) HR_{adj}= 1.7 (95% CI: 1.0–2.8) were observed in the patients. Excluding melanoma and other malignant neoplasms of skin reduced the rate of SM in patients (relative to comparators) although it remained statistically significant HR_{adj}= 1.2 (95% CI: 1.0–1.4) (Table 5).

Table 1
Characteristics of mantle cell lymphoma (MCL) patients and matched general population comparators in Sweden between 2000 and 2017§.

	MCL patients	Comparators	*P*-value
	N (Col %)	N (Col %)	
Overall	1 452	13 992	
Median age at MCL diagnosis/matching (range)	70.0 (22.2–96.4)	69.7 (21.9 – 97.0)	
Age categories at diagnosis/matching			
< 60	267 (18.4%)	2 677 (19.1%)	
60–69	460 (31.7%)	4 505 (32.2%)	
70–79	484 (33.3%)	4 668 (33.4%)	
≥ 80	241 (16.6%)	2 142 (15.3%)	0.6
Sex			
Female	397 (27.3%)	3 832 (27.4%)	
Male	1 055 (72.7%)	10 160 (72.6%)	0.9
Year of diagnosis/matching			
2000–2004	287 (19.8%)	2 743 (19.6%)	
2005–2009	340 (23.4%)	3 270 (23.4%)	
2010–2014	503 (34.6%)	4 853 (34.7%)	
2015–2017	322 (22.2%)	3 126 (22.3%)	0.9
Charlson Comorbidity Index			
0	787 (54.2%)	8 641 (61.8%)	
1	427 (29.4%)	3 393 (24.2%)	
≥ 2	238 (16.4%)	1 958 (14.0%)	< 0.01
Highest achieved education level			
≤ 9	507 (34.9%)	5 209 (37.2%)	
10–12	573 (39.5%)	5 412 (38.7%)	
≥ 13	356 (24.5%)	3 177 (22.7%)	
Missing	16 (1.1%)	194 (1.4%)	0.2
Marital status			
Never married	522 (36.0%)	5 596 (40.0%)	
Married	926 (63.8%)	8 338 (59.6%)	
Missing	4 (0.3%)	58 (0.4%)	< 0.01
History of cancer			
No	1 165 (80.2%)	11 998 (85.7%)	
Yes	287 (19.8%)	1 994 (14.3%)	< 0.01

§: Patients (and comparators) leaving the follow-up during the first year did not contribute to the final study population

Table 2
Total number, incidence rate (IR), and hazard ratio (HR) with 95% confidence interval (CI) of malignancies occurring in mantle cell lymphoma (MCL) patients versus matched general population comparators, twelve months from the diagnosis (matching) date in Sweden between 2000 and 2017.

	MCL patients		Comparators		HR_{adj} (95% CI)*	*P* * *
	Events$^{\alpha}$	IR (95% CI) per 1000 persons-years	Events$^{\alpha}$	IR (95% CI) per 1000 persons-years		
Overall	264	40.3 (35.6; 45.5)	2 601	27.4 (26.4; 28.5)	1.6 (1.4; 1.8)	
Age categories at diagnosis/matching						
< 60	38	19.6 (13.9; 26.9)	357	14.6 (13.1; 16.2)	1.4 (1.0; 2.0)	
60–69	95	42.6 (34.5; 52.1)	932	28.2 (26.4; 30.1)	1.6 (1.3; 2.0)	
70–79	99	55.7 (45.3; 67.8)	1 024	35.9 (33.7; 38.1)	1.6 (1.3; 2.0)	
≥ 80	32	53.5 (36.6; 75.5)	288	32.5 (28.9; 36.5)	1.7 (1.2; 2.4)	0.3
Sex						
Female	57	31.0 (23.5; 40.2)	559	21.8 (20.0; 23.6)	1.5 (1.2; 2.0)	
Male	207	44.0 (38.2; 50.4)	2 042	29.5 (28.2; 30.8)	1.6 (1.4; 1.8)	0.9
Year of diagnosis/matching						
2000–2004	49	29.3 (21.6; 38.7)	816	26.1 (24.3; 27.9)	1.4 (1.0; 1.8)	
2005–2009	82	41.7 (33.2; 51.8)	809	28.3 (26.3; 30.3)	1.6 (1.3; 2.0)	
2010–2014	101	45.1 (36.8; 54.9)	774	28.1 (26.2; 30.2)	1.7 (1.3; 2.0)	
2015–2017	32	47.9 (32.8; 67.6)	202	27.1 (23.5; 31.1)	1.8 (1.2; 2.5)	0.3
Charlson Comorbidity Index						
0	153	36.6 (31.0; 42.9)	1 663	25.0 (23.8; 26.2)	1.6 (1.4; 1.9)	
1	76	45.7 (36.0; 57.1)	620	31.7 (29.2; 34.3)	1.5 (1.2; 1.9)	
≥ 2	35	49.8 (34.7; 69.2)	318	36.4 (32.5; 40.6)	1.4 (1.0; 2.1)	0.5
Highest achieved education level						
≤ 9	92	47.8 (38.5; 58.6)	966	27.8 (26.1; 29.6)	1.8 (1.4; 2.2)	
10–12	101	37.0 (30.1; 44.9)	1 048	27.9 (26.3; 29.7)	1.4 (1.2; 1.8)	
≥ 13	70	38.8 (30.2; 49.0)	565	26.1 (24.0; 28.4)	1.6 (1.2; 2.1)	0.1
Missing	1	11.8 (0.3; 65.6)	22	21.0 (13.2; 31.8)	-	
Marital status						
Never married	74	35.3 (27.7; 44.3)	914	26.2 (24.6; 28.0)	1.5 (1.2; 1.9)	
Married	190	43.0 (37.1; 49.6)	1 681	28.2 (26.9; 29.6)	1.6 (1.4; 1.9)	0.5
Missing	-	-	6	12.1 (4.4; 26.3)	-	
History of cancer						
No	206	37.7 (32.8; 43.3)	2 215	26.3 (25.2; 27.4)	1.5 (1.3; 1.8)	
Yes	58	53.4 (40.5; 69.0)	386	36.3 (32.8; 40.2)	1.6 (1.2; 2.1)	0.9

α: All malignancies occurring during the follow-up and considering only the first event of each type of malignancy, HR_{adj}: Hazard ratio (and 95% confidence interval) mutually adjusted for age at diagnosis, year of diagnosis/matching, sex and a time-dependent variable indicating the order of the event, * Comparators are the reference group, * * p-value for interaction, IR: Unadjusted incidence rates.

Sensitivity analyses showed that varying the start of follow-up (from 12 to 6, 18, or 24 months from the diagnosis date) did not impact the results (Table S2). In an additional sensitivity analysis limiting the study follow-up to focus exclusively on the occurrence of the initial secondary malignancy, the higher rate of SM in patients versus comparators, HRadj= 1.6 (95% CI: 1.4–1.8) remained consistent.

4. Discussion

With improvements in the overall survival of MCL patients, treatment-related long-term outcomes have become a major concern. The number of long-term survivors is expected to further increase, and the burden of SM could considerably shorten the survival for these patients. We demonstrated a 60% increase in the rate of SM in MCL patients relative to age-, sex-, and calendar year-matched general population comparators. Among patients, first-line treatments with particularly R-bendamustine, ibrutinib and lenalidomide were independently associated with an increased risk of SM though only a few patients were included in the latter two groups. The number of patients with SM is limited in absolute numbers, partially explained by a higher mortality in MCL patients.

The increased rate of SM observed in our study is higher than that reported in previous studies. In a Korean cohort of 439 MCL patients followed for 948 person-years, 23 patients later developed at least one SM. The incidence of SM per 100 person-years was 2.43 (95%CI: 1.57–3.58) [14] versus 4.03 (95%CI: 3.56–4.55) per 100 person-years in our report, with a five-year cumulative incidence of 12% [14] compared to 17.6% reported in our study. Among 3149 US MCL patients diagnosed between 1992 and 2011, 261 (8.3%) developed 287 SM with an observed/expected (O/E) ratio of 1.32 (95% CI: 1.17–1.48) [13] to be compared to the 16% of patients with SM seen in our series. The reduced risk observed compared to our study may be related to the limited follow-up in the US study (median: 2.5 [13] versus 5.6 years) and in the Korean study (maximum 10-year follow-up [14] vs. 19 years). The availability of nation-wide well-maintained registers in Sweden allowed for longer follow-up.

Melanoma and other malignant neoplasms of the skin showed three times higher rates in patients versus comparators. A sensitivity analysis excluding melanoma and other malignant neoplasms of skin lowered the overall rate, although the risk remained elevated. In addition to skin cancer, the highest rates were observed for neoplasms of uncertain/unknown behaviour and hematopoietic/lymphoid malignancies (excluding MCL). These findings are consistent with previous reports [12,13]. While causation cannot be established due to the study's observational nature, we speculate that the skin malignancy increase may be due to surveillance bias or immunosuppressive drug effects. In addition, Sweden's relatively high melanoma incidence due to its fair-skinned population and high ultra-violet radiation levels during the summer months may also contribute. For hematopoietic malignancies, possible explanations include cell lineage transformations or diagnostic misclassifications. Due to the retrospective design, we cannot investigate these further, so these findings should be interpreted with this limitation in mind.

A prior investigation has documented an elevated occurrence of urological malignancies when employing the hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen alternated with methotrexate and cytosine arabinoside (Hyper-CVAD/M-A) [28]. However, our current study did not observe a similar trend. It is plausible that improvements in treatment approaches over the past two decades, incorporating various immunomodulatory drugs and employing lower chemotherapy dosages compared to earlier years, may confer a protective effect against the development of these malignancies.

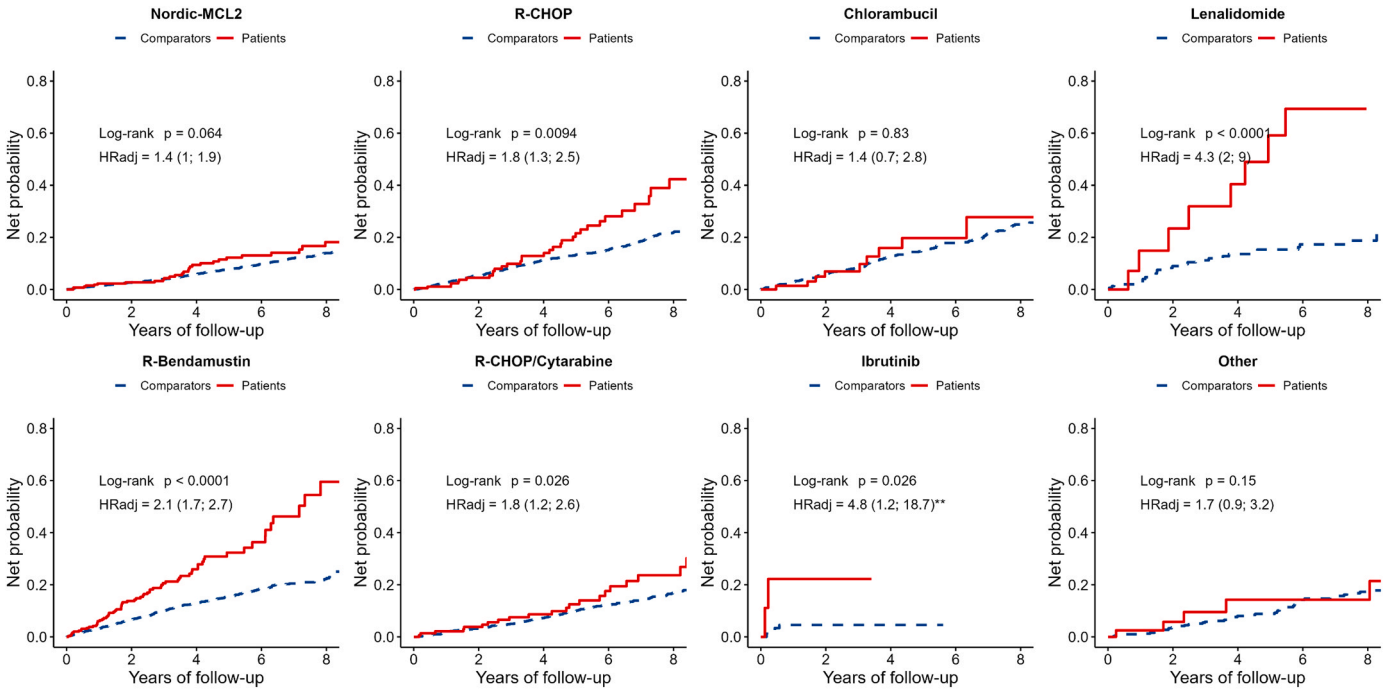

Fig. 2. Net probability (1-Kaplan Meier) of malignancy occurrence among mantle cell lymphoma (MCL) patients and their respective matched population comparators, twelve months from the diagnosis (matching) date stratified by the first-line treatment that the patients received. Individuals were censored at death. * *: *Model adjusted only for sex. HR_{adj}: Hazard ratio (and 95% confidence interval) from Andersen–Gill regression model adjusted for age at diagnosis, year of diagnosis/matching, sex and a time-dependent variable indicating the order of the event. Comparators are the reference group. R-bendamustine: rituximab-bendamustine, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone. Nordic-MCL2: R-CHOP/R-cytarabine, high dose treatment and consolidation with an autologous stem cell transplant. Nordic-MCL2 included five cases of CHOP/DHAX treatment. Other treatments include: VADRIAC (Vincristine, Cyclophosphamide and Doxorubicin), BAC (Bendamustine and Cytarabine), Ixoten (trofosfamide), R-Bendamustine and R-Cytarabine, Rituximab/Ribovact, and Sendoxan.*

The observed increased rate of SM was largely driven by the direct and indirect effects of Nordic-MCL2, R-CHOP, R-CHOP/Cytarabine, and R-bendamustine which together accounted for more than 50% of all first-line treatments. The Nordic-MCL2 and R-CHOP were more commonly used in younger and fitter patients (generally aged <65 years). The improved outcomes in these patients align with longer life expectancy and delayed treatment-related effects. R-bendamustine on the other hand is used more in elderly patients and has been associated with an increased risk of SM in prior investigations [29,30]. In a follow-up study on delayed toxicity of bendamustine, 25 SM in 23 previously treated relapsed/refractory NHL patients were observed after 8.9 years median follow-up [6], though this later study may not be appropriate to extrapolate to the use of bendamustine in first-line treatment setting as in our case. In a recent study, 6 SM were reported among 57 elderly, previously untreated patients, treated with a combination of rituximab, bendamustine, and low-dose cytarabine (R-BAC) [31]. However, R-BAC involves a less intensive bendamustine regimen and often consists of four cycles instead of the six used in R-bendamustine. The biological mechanism of the carcinogenic effect of (R)-bendamustine is not clearly understood, however its chemical structure suggests it has alkylating and anti-metabolite activities and it is known that bendamustine induces dose-dependent DNA damage [5]. Bendamustine also leads to marked reductions in CD3 + and CD3 +CD4 + T cells during induction [29] and the decreased T-cell activity [32] may increase the risk of SM with R-bendamustine compared to R-CHOP.

Only a few patients were treated with ibrutinib (n = 9) or lenalidomide (n = 16) as first-line treatment in our study. Both treatments were independently associated with two to four-fold increased risk, however the small number of patients undergoing those treatments in first-line in Sweden and the resulting large imprecision precludes any firm conclusions. In addition, we suspect these patients were also more likely to be included in clinical trials and potentially followed more carefully with radiology scans potentially identifying more malignancies thus inducing a possible surveillance bias. Disregarding these patients, given their small number and few observed events, is unlikely to alter the current study results.

Having a first-degree family history of lymphoma was associated with a slightly increased rate of SM relative to patients without family history of lymphoma. Increased risk of SM in NHL survivors with a positive family history of any cancer (p-trend <0.001) has also been reported earlier [11]. It is generally accepted that the occurrence of SM is attributed mostly to the late effects of treatments, but is also likely to be caused by genetic and environmental factors [33–35]. Given that only a few studies focused on the genetic factors of SM in lymphomas, further studies are needed to disentangle the genetic factor effects and assess patient's susceptibility to damage from chemotherapy and/or targeted drugs.

Even though MCL patients have higher rates of SM compared to their matched comparators, the absolute risk of developing a SM is reduced by the high mortality in these patients i.e., most patients will die from MCL before "having the chance" to develop a SM. In fact, in most patients, the final cause of death was MCL as shown in a prior study [36]. In the case of a second malignancy the patients were still mainly at risk of dying from the underlying lymphoma, perhaps since the lymphoma disease is recurring in its nature and also that the second malignancy might preclude further lymphoma treatment. While prognosis is improving, the risk of SM will likely be a growing issue in the future and preventive measures including a greater awareness of the risks among clinicians, transition to drugs with less risks of SM and potentially screening could be relevant future actions.

One of the advantages of studying risk in comparison to MCL-free, age, sex and calendar year matched general population comparators is that the excess burden from the MCL and its treatment can be disentangled from the usual expected risk in an elderly population. Further, a long tradition of collecting data in quality registers in Sweden enables

Table 3
Description and hazard ratio (with 95% confidence interval CI) of events (secondary malignancies) according to demographic characteristics and comorbidities among mantle cell lymphoma (MCL) patients in Sweden, twelve months from the diagnosis date.

	MCL patients	Patients with events	Total events	HR_{adj} (95% CI)	Trend test p value
Overall	1 452	230	264		
Age categories at diagnosis/matching					
< 60	267	33	38	1.0 (reference)	
60–69	460	78	95	2.3 (1.5; 3.6)	
70–79	484	87	99	3.2 (2.1; 4.9)	
≥ 80	241	32	32	3.6 (2.2; 5.9)	< 0.001
Sex					
Female	397	53	57	1.0 (reference)	
Male	1 055	177	207	1.5 (1.1; 2.0)	0.006
Year of diagnosis/matching					
2000–2004	287	43	49	1.0 (reference)	
2005–2009	340	67	82	1.3 (0.9; 1.9)	
2010–2014	503	90	101	1.5 (1.0; 2.2)	
2015–2017	322	30	32	2.1 (1.3; 3.4)	0.012
Charlson Comorbidity Index					
0	787	133	153	1.0 (reference)	
1	427	69	76	1.0 (0.8; 1.4)	
≥ 2	238	28	35	1.1 (0.7; 1.6)	0.864
Highest achieved education level					
≤ 9	507	82	92	1.0 (reference)	
10–12	573	89	101	0.9 (0.7; 1.2)	
≥ 13	356	58	70	1.0 (0.7; 1.4)	0.819
Missing	16	1	1	-	
Marital status					
Never married	522	62	74	1.0 (reference)	
Married	926	168	190	1.1 (0.8; 1.5)	0.420
Missing	4			-	
History of cancer					
No	1 165	183	206	1.0 (reference)	
Yes	287	47	58	1.3 (0.9; 1.7)	0.121
Family history of lymphoma					
No	1 372	207	236	1.0 (reference)	
Yes	80	23	28	1.7 (1.1; 2.5)	0.009

HR_{adj}: Hazard ratio (and 95% confidence interval) mutually adjusted for age at diagnosis, year of diagnosis, sex and a time-dependent variable indicating the order of event during follow-up.

the use of high-quality data sets including clinical characteristics, treatments, and long-term follow-up information. The rather small number of SM and the limited survival time of MCL patients hampered risk estimates for all cancer sites even after considering all SM during the

Table 4
Description and hazard ratio with 95% confidence interval (CI), of secondary malignancies occurrence according to clinical characteristics and treatment categories among mantle cell lymphoma (MCL) patients in Sweden, twelve months from the diagnosis date.

	MCL patients	Patients with events	Total events	HR_{adj} (95% CI)
Stage				
Ann Arbor I	98	20	25	1.0 (reference)
Ann Arbor II	149	20	22	0.7 (0.4; 1.3)
Ann Arbor III	191	48	58	1.4 (0.8; 2.3)
Ann Arbor IV	982	138	155	0.9 (0.6; 1.4)
Missing	32	4	4	1.0 (0.3; 2.7)
MIPI				
Low risk (<5.7)	172	18	23	1.0 (reference)
Intermediate risk (5.7–6.1)	364	68	83	1.3 (0.8; 2.3)
High risk (>6.1)	425	59	62	1.2 (0.7; 2.1)
Missing	491	85	96	1.5 (0.8; 2.6)
Primary treatment Immunochemotherapy				
No	64	9	10	1.0 (reference)
Yes	1 075	179	208	1.5 (0.8; 2.8)
Missing*	313	42	46	1.1 (0.5; 2.2)
Radiotherapy				
No	921	155	177	1.0 (reference)
Yes	109	17	22	0.8 (0.5; 1.4)
Missing*	422	58	65	0.7 (0.5; 1.1)
Treatment consolidation				
Non-ASCT	764	131	147	1.0 (reference)
ASCT	296	38	47	1.0 (0.6; 1.4)
Missing*	392	61	70	0.9 (0.6; 1.4)
Type of immunochemotherapy treatment				
Nordic-MCL2 * *	273	35	40	1.0 (reference)
Chlorambucil	84	9	12	1.2 (0.6; 2.5)
Cytarabine[α]	14	≤ 3	≤ 3	1.3 (0.4; 4.1)
FC	21	4	4	0.9 (0.3; 2.6)
R-Bendamustine	301	69	75	2.0 (1.3; 3.2)
R-CHOP	200	33	42	1.5 (0.9; 2.3)
R-CHOP/Cytarabine	149	24	30	1.2 (0.7; 2.0)
Missing*	367	44	48	0.9 (0.6; 1.3)
Other* **	43	9	10	1.4 (0.8; 2.7)
Lenalidomide				
No	1 023	156	179	1.0 (reference)
Yes	16	8	9	2.3 (1.3; 4.2)

(*continued on next page*)

Table 4 (*continued*)

	MCL patients	Patients with events	Total events	HR_{adj} (95% CI)
Missing	413	66	76	1.0 (0.7; 1.5)
Ibrutinib[α]				
No	1 032	163	187	1.0 (reference)
Yes	9	≤ 3	≤ 3	4.2 (1.7; 10.9)
Missing	411	65	75	1.0 (0.6; 1.5)
Treatment with alkylating agent				
No[αβ]	14	≤ 3	≤ 3	1.0 (reference)
Yes[£]	1028	174	203	1.1 (0.4; 3.3)
Missing	367	44	48	0.7 (0.2; 2.2)

HR_{adj}: Hazard ratio (and 95% confidence interval) adjusted for age at diagnosis, year of diagnosis, sex and a time-dependent variable indicating the order of the event, * Treatment information was missing particularly in the earlier calendar period (before year 2007), * *: Including five cases of CHOP/DHAX treatment, * ** : Other treatments include: VADRIAC (Vincristine, Cyclophosphamide and Doxorubicin), BAC (Bendamustine and Cytarabine), Ixoten (trofosfamide), R-Bendamustine and R-Cytarabine, Rituximab/Ribovact, and Sendoxan. ASCT: autologous hematopoietic stem cell transplantation, (R-)CHOP: (Rituximab-) Cyclophosphamide, doxorubicin, vincristine, prednisone. FC: Fludarabine, cyclophosphamide; Nordic-MCL2: R-CHOP/R-cytarabine, high dose treatment and consolidation with an autologous stem cell transplant. α: For reasons related to data protection and confidentiality, the exact number cannot be specified; β: Treatment containing no alkylating agent includes: Cytarabine; £ : Treatments containing at least one alkylating agent are: Nordic-MCL2, Chlorambucil, FC (Fludarabine, cyclophosphamide), R-Bendamustine, R-CHOP, R-CHOP/ Cytarabine

patient's lifetime. Further on, we only stratified patients by first-line treatment concept due to the limited number of events, especially for newer agents. Finally, our study did not include information on common cancer risk factors, neither smoking, obesity, environmental nor genetic factors since that information was not routinely collected. Thus, further research is still needed to assess such associations for enabling preventive measures and adapted follow-up strategies for MCL patients at high risk for SM to achieve a better outcome.

In summary, the intensive treatments needed for long-term remissions are a concern. Our study suggests that better surveillance of lymphoma patients, especially if treated with R-bendamustine, Bruton tyrosine kinase inhibitors and lenalidomide regarding specifically melanoma, skin and other haematological malignancies is needed. However, it is worth noting that the lenalidomide and ibrutinib in first line treatment modalities had limited representation within the studied population. More studies are also warranted to better assess the confounding factors behind the excess risk and to evaluate measures of prevention.

Author's contribution

IG, KDA, SEk, KES, MJ, and SP designed the study. KDA and SEk independently performed and reviewed the statistical analyses. SEk and SEl critically reviewed the statistical methods. KDA and IG wrote the paper. All authors interpreted the data, provided input for the manuscript, and approved the final version.

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Declaration of Competing Interest

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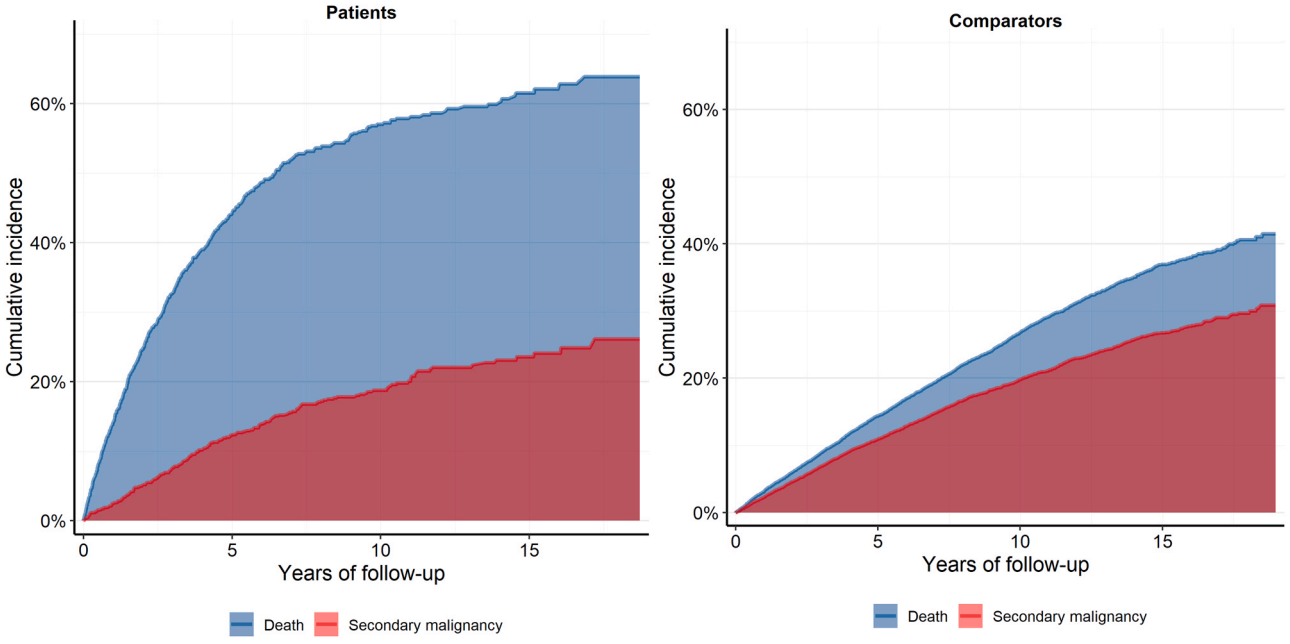

Fig. 3. Cumulative incidence (in percent) of secondary malignancies, among mantle cell lymphoma patients (left panel) and comparators (right panel), accounting for the competing risk of death from any cause.

Table 5
Hazard ratios with 95% confidence intervals (CI) for specific type of secondary malignancy diagnosis presented according to International Classification of Diseases 10th version (ICD-10) codes, for mantle cell lymphoma (MCL) patients and comparators, twelve months from the diagnosis (matching) date.

		Patients	Comparators	HR*§ (95% CI)	HR_{adj}*§ (95% CI)
Type of malignant neoplasms	**ICD-10**	**Events**	**Events**		
All malignant neoplasms	C00 – D48	264	2 601	1.5 (1.3; 1.7)	1.6 (1.4; 1.8)
All malignant neoplasms (excluding melanoma and skin cancers C43 - C44)	C00 – D48	156	2 039	1.6 (1.0; 1.4)	1.2 (1.0; 1.4)
Neoplasms of uncertain or unknown behaviour	D37 – D48	9	30	4.8 (2.3; 10.1)	5.0 (2.4; 10.5)
Melanoma and other malignant neoplasms of skin	C43 – C44	109	626	2.7 (2.2; 3.3)	2.9 (2.4; 3.5)
Melanoma	C43	20	177	1.7 (1.1; 2.7)	1.7 (1.1; 2.7)
Other malignant neoplasms of skin	C44	90	451	3.1 (2.5; 3.9)	3.5 (2.8; 4.5)
Malignancies of lymphoid, hematopoietic, and related tissue* *	C81 – C96	17	162	1.5 (0.9; 2.5)	1.7 (1.0; 2.8)
Lip, oral cavity, and pharynx	C00 – C14	6	42	2.7 (0.9; 6.0)	2.4 (0.9; 6.1)
Respiratory and intrathoracic organs	C30 – C39	18	192	1.4 (0.8; 2.2)	1.4 (0.9; 2.3)
Urinary tract	C64 – C68	17	202	1.3 (0.8; 2.1)	1.3 (0.8; 2.2)
Digestive organs	C15 – C26	38	569	0.9 (0.7; 1.3)	1.0 (0.7; 1.4)
Male genital organs	C60 – C63	38	569	1.0 (0.7; 1.4)	1.0 (0.7; 1.4)
Breast	C50 – C50	5	96	0.8 (0.3; 1.9)	0.7 (0.3; 1.8)
Bone and articular cartilage$^{\alpha}$	C40 – C41	0	≤ 3	-	-
Mesothelial and soft tissue$^{\alpha}$	C45 – C49	≤ 3	16	-	-
Eye, brain and other parts of central nervous system	C69 – C72	0	26	-	-
Thyroid and other endocrine glands$^{\alpha}$	C73 – C75	≤ 3	21	-	-
Ill-defined, secondary, and unspecified sites	C76 – C80	0	51	-	-
Female genital organs$^{\alpha}$	C51 – C58	≤ 3	60	-	-

HR_{adj}: Hazard ratio (and 95% confidence interval) adjusted for age at diagnosis, year of diagnosis/matching, sex and a time-dependent variable indicating the order of the event, * : for cancers with ≥ 5 events among patients, §: Comparators group is the reference group, * * Removing MCL as secondary cancer, α: For reasons related to data protection and confidentiality, the exact number cannot be specified.

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Data Availability

The data in our study results from linkages of nationwide registers as described in the method section. Restrictions apply for the availability of these data according to the national data protection legislation. Data are available from the authors with the permission of the Swedish Authority for Privacy Protection. Interested researchers can approach the corresponding author (KDA, kossi.dovene.abalo@ki.se) or the principal investigator (IG, ingrid.glimelius@igp.uu.se) for sharing data as part of collaborative research projects (if not overlapping with ongoing research projects). The statistical analysis plan is made available for anyone.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113403.

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