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Richter syndrome epidemiology in a large population based chronic lymphocytic leukemia cohort from Norway

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ABSTRACT

Background: Transformation to aggressive lymphoma (Richter syndrome, RS) occurs in a substantial subset of patients who must discontinue targeted therapy for chronic lymphocytic leukemia (CLL). RS has an extremely poor prognosis.

Methods: Using the nation-wide database of The Cancer Registry of Norway of 7664 CLL patients registered between 1953–2012, we identified 107 patients experiencing RS.

Results: Seventy seven (72%) of RS patients were identified among 2631 CLL patients diagnosed between 2003–2012; diffuse large B-cell lymphoma (DLBCL) was identified in 65 (84%), Hodgkin lymphoma (HL) in 12 (16%) patients and the diagnosis was confirmed in 50 (65%) available biopsy specimens. The incidence rate in this period was 4.7/1000 person-years (95% CI: 3.8–5.9). The median survival from CLL diagnosis was 1.7 years (95% CI: 0.34–2.3) for RS patients while it was 10.3 years (95% CI: 9.5–10.9) for the remaining CLL patients. Male gender predominated among RS patients (69%) compared to CLL population (58%) and RS patients were diagnosed with CLL at a significantly younger age than the remaining patients (65 vs. 72 years). Median time from diagnosis of CLL to RS was 2 years (Range, 0–13 years). No CLL treatment was administered in 25 (33%) patients prior RS diagnosis; a median of 1 treatment line was administered to pretreated patients. The median duration of survival after RS diagnosis was 27 months (95% CI; 9–88).

Conclusions: Collectively, RS was a rare complication of CLL in the chemoimmunotherapy era, occurred early in the CLL course in younger, and both treatment naïve and pretreated patients, and shortened survival substantially.

1. Background

Richter syndrome (RS); the occurrence of an aggressive lymphoma in patients with chronic lymphocytic leukemia (CLL) remains one of the reasons for disease progression on novel agents. In contrast to the potent and sustained efficacy of current treatment even in high risk CLL, median survival of patients with RS has been as short as 9 months, and even shorter in patients who transform on ibrutinib [1–7]. Thus, RS remains a major challenge in the changing landscape of the CLL therapy.

Morphologically, the transformed lymphoma is diffuse large B-cell lymphoma (DLBCL) or, less frequently, Hodgkin lymphoma (HL) [8–10].

The incidence of RS is reported to be 1–10%, but the reports on incidence are derived from selected institutional populations and only some of them exclude clonally unrelated lymphoma [11–14]. The incidence of RS has never been assessed in an unselected population.

Next generation genome sequencing has explored the genomic landscape of CLL as well as RS [9,15,16]. However, the mechanisms leading to transformation still remain elusive.

Clinical and biological risk factors for transformation to DLBCL are based on retrospective institutional patient cohorts [13,17–19]. In the case of Hodgkin lymphoma, only small institutional series or case reports describing clinical and molecular features are available [20].

Abbreviations: CLL, chronic lymphocytic leukemia; RS, Richter syndrome; DLBCL, diffuse large B-cell lymphoma; RS/DLBCL, Richter syndrome with DLBCL histology; RS/HL, Richter syndrome with HL histology

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We took advantage of an almost complete, population-based CLL population at The Cancer Registry of Norway and assessed the incidence, clinical, biological and histological features of RS in CLL patients diagnosed between 1953–2012. We have described incidence and survival, as well as demographic trends of this particular CLL population in a previous report [21].

2. Methods

2.1. Patients and materials

We took advantage of a CLL cohort of 766 patients registered at The Cancer Registry of Norway between 1953–2012 [21].The database was matched to information in The Norwegian Cause of Death Registry at Statistics Norway and The National Registry on Vital Status and Migration updated per 30 June 2018.

We initially screened broadly all 7664 patients for a consecutive diagnosis of lymphoproliferative disease different from CLL registered by 31 Dec 2017 and extracted 1360 patient reports. We reviewed their pathology reports and identified 111 reports indicating RS. We excluded 26 patients incorrectly registered as CLL/SLL, even though the original pathology report indicated mantle-cell lymphoma, marginal zone B-cell lymphoma and CD10+ small B-cell lymphoma, or hairy-cell leukemia. The remaining 1223 reports concluded with small lymphocytic lymphoma, e.g. CLL. The diagnosis of RS was based on a biopsy confirmation of DLBCL and Hodgkin lymphoma.

The study hematopathologist (UR) reviewed pathology from the initial diagnosis and transformation according to the WHO criteria in 69 available cases [1].

The clinical characteristics, age, sex, lymphoproliferative disease in first grade relative, Eastern Cooperative Oncology Group (ECOG) performance status, Binet stage, B-symptoms, lymphadenopathy, splenomegaly, hepatomegaly, autoimmune phenomenon, absolute leucocyte count, hemoglobin, lactate dehydrogenase (LDH), IGHV features and karyotype at CLL diagnosis, and CLL treatments were recorded, however the retrieval grade was low and analysis omitted.

We received data on nation wide DLBCL incidence from the Cancer Registry of Norway.

The study was approved by the Regional Committee for Medical and Health Research Ethics South East Norway (2014/427/REK Sør-Øst).

2.2. Definitions and statistical analysis

We divided 60 years of CLL registration into 6 decades for trends and difference analysis.

Transformation rates were calculated using a person-years approach, in which number of documented cases of transformations was divided by total person-years of follow up.

CLL patients without transformation were censored at the time of death or last follow up (30 June 2018). Eleven patients emigrated and were censored at the time they left the country. Time to RS was measured from the time of diagnosis of CLL to the date of the biopsy showing DLBCL or Hodgkin lymphoma. The reversed Kaplan-Meyer method was used to calculate follow-up time.

The OS was calculated from the time of diagnosis of CLL to the date of death or last follow up. The Kaplan-Meier method, corrected for immortal bias, was used to calculate survival. Age- and sex-stratified log-rank test was used in comparative survival analysis.

We showed earlier that the survival of CLL patients throughout 60 years of registration differs considerably and since we identified few patients with RS before 2003, we found a comparative analysis of survival within 2003–2012 more appropriate [21].

We calculated a median survival of RS patients from the time of diagnosis of RS to the date of death or the end of the study.

Continuous and categorical variables were compared using Student-t test and “chi square” test, respectively. The proportion of males and females was compared using two-sample test of proportions. All tests were two-sided.

Statistical analyses were performed using STATA version 15.1 (StataCorp, College Station, Texas, USA).

3. Results

3.1. Patients

Among 7638 CLL patients diagnosed between 1953–2012, after median follow-up of 5.2 years, we identified 111 cases with pathology report indicating Richter syndrome. The study hemathopathologist reviewed 69 (62%) biopsies and excluded two cases in which the diagnosis of RS was incorrect and was better characterized as CLL with increased proportion of prolymphocytes and paraimmunoblasts. We excluded one further case due to missing both clinical information and biopsy specimen. Thus, 108 patients with RS were included in this study; 91 (84%) had DLBCL, 16 (15%) had HL and 1 (1%) patient had a composite lymphoma, e.g. both DLBCL and Hodgkin lymphoma within the same biopsy.

3.2. The Incidence of Richter syndrome

The incidence of RS was highest in the 2631 patients diagnosed with CLL between 2003–2012 (incidence rate 4.7/1000 person-years; 95% CI: 3.8–5.9) and was significantly ($p < 0.001$) higher than the incidence rate in 1548 patients diagnosed with CLL between 1993–2002 (incidence rate 1.9/1000 person-years; 95%CI: 1.2–3.0); incidence rate ratio 2.5 (95%CI: 1.5–4.3).

The incidence rate of RS/DLBCL in CLL patients diagnosed between 2003–2012 was 4/1000 person-years (95%CI: 3.1–5.1) and was 2.6 times higher (incidence rate ratio; 95%CI: 1.5–5; $p < 0.001$) than the incidence rate of RS/DLBCL in CLL patients diagnosed between 1993–2002 (1.5/1000 person-years, 95%CI: 0.1–2.5).

Table 1 depicts prevalence development through the whole study period and shows a very low RS detection rate until 2003. In 5007 patients diagnosed with CLL between 1953–2002, 31 (0.6%) cases with RS were registered, while in 2631 CLL patients diagnosed with CLL between 2003–2012, 77 (3%) cases with RS were registered. The study hemathopathologist confirmed histological aggressive lymphoma diagnosis by reviewing 50 (65%) available biopsies from patients diagnosed with CLL between 2003–2012.

Only two patients diagnosed with CLL before 1983 were later registered with RS; and the first case with RS was registered in 1985 in a patient diagnosed with CLL the same year.

3.3. Proportion of RS in total DLBCL burden in Norway

In total, 4810 (2693 men; 56%) patients older than 30 were registered with DLBCL at The Cancer Registry of Norway between 2003–2017; thus 76 (51 men; 67%) patients with RS/DLBCL diagnosed in the same period represent 1.6% of cases. The proportion of men was higher in RS/DLBCL patients than among the remaining DLBCL patients ($p = 0.0552$). Of 740 males aged 60–69 registered with DLBCL, 20 (2.7%) were RS/DLBCL.

3.4. Time from diagnosis of CLL to transformation to Richter syndrome

Among 77 patients with CLL diagnosed between 2003–2012, CLL and RS/DLBCL were diagnosed simultaneously in six patients, and one patients was diagnosed with RS within 3 months of the CLL diagnosis.

In the remaining 70 patients, the median time from diagnosis of CLL to RS was 48 months (range, 4–157 months); in 60 patients with RS/DLBCL the median elapsed time from the diagnosis of CLL was 50 months (Range: 4–157), and in 10 RS/HL patients it was 39 months (Range: 6–99). The difference was not statistically significant.

Table 1
Reporting of Richter syndrome in CLL patients in Norway between 1953–2017 and characteristics of patients registered with CLL between 2003–2012. One patient with composite lymphoma (both DLBCL and HL in biopsy) excluded. CLL; chronic lymphocytic leukemia DLBCL; Diffuse large B-cell lymphoma HL; Hodgkin lymphoma.

CLL (N = 7638)						
	Richter syndrome					
	Yes (N = 107)				No (N = 7530)	
	DLBCL		HL			
Number of patients	№	%	№	%	№	%
Total	91	100	16	100	7530	100
Year of CLL diagnosis						
1953-1962	0		0		351	5
1963-1972	0		0		641	9
1973-1982	5	6	0		1129	15
1983-1992	6	7	1	6	1326	18
1993-2002	15	17	3	19	1529	20
2003-2012	65	71	12	75	2554	34
Characteristics of patients, 2003-2012						
Number of patients	65	100	12	100	2554	100
Sex						
Male	44	68	9	75	1467	57
Age at CLL diagnosis						
0-59	21	32	1	8	457	18
60-69	24	37	5	42	689	27
70-79	16	25	5	42	730	29
80+	4	6	1	8	678	27
Median age at CLL diagnosis	Years		Years		Years	
	65		69		72	
Range	42-86		51-83		35-102	

Of the 70 patients diagnosed with RS more than three months beyond their CLL diagnosis, data on CLL treatment were available in 63 (90%) patients. Fig. 1 illustrates that both treatment-naïve patients and pretreated patients tended to be diagnosed with RS during the first few years of CLL duration. RS occurred prior to treatment in 18 (29%; 15 DLBCL, 3 H L) patients and following treatment in 45 (71%; 39 DLBCL, 6 H L) patients. The median time from CLL diagnosis to RS was 45 months (range, 4–157) in treatment-naïve patients and 46 months (range, 5–130 months) in pretreated patients.

3.5. Characteristics of 77 patients experiencing Richter syndrome between 2003-2017

3.5.1. Demographic features

The median age at CLL diagnosis was 65 years (range, 42–86) in the 77 patients experiencing RS, while it was 71 years (range, 34–102 years) in the 2554 remaining patients ($p < 0.0001$). The median age at CLL diagnosis was 65 years (Range, 42–86) in 65 patients with DLBCL, and 69 years (Range, 51–83) in 12 patients with HL ($p = 0.15$). The median age at CLL diagnosis was 68 years (Range; 50–83) in 10 patients diagnosed with RS within the first 6 months of CLL treatment course and 65 years (42–86) in 67 remaining patients.

The median age at CLL diagnosis was 63 years (range, 42–86) in 45 pretreated patients and 70 years (range, 48–80) in 18 treatment-naïve patients ($p = 0.12$), considering 63 patients diagnosed with RS beyond 3 months of CLL duration with available treatment record.

Among the 77 patients experiencing RS, 53 (69%) were men, while 1468 (58%) were men among 2554 remaining patients ($p = 0.05$). The male predominance was most pronounced among those who transformed to HL; only three were women. We found persisting male predominance in the pretreated vs. the treatment-naïve group (72% vs. 63% males) and in 67 patients (72% men) diagnosed with RS after CLL duration longer than 6 months, while in 10 patients diagnosed with RS early in the CLL course (within 6 months), five (50%) were women. We did not find any significant difference in sex proportion between groups, possibly due to small number of patients.

3.5.2. Prior CLL treatment

Detailed treatment log was available in 38 (84%) of 45 patients diagnosed with RS after 3 months of CLL duration who had received CLL treatment. They received a median of one treatment line prior RS diagnosis (Range; 1–5).Twenty three (61%) had received only one line of treatment prior to RS diagnosis, nine (24%) two lines of treatment.

3.6. Survival of patients experiencing Richter syndrome between 2003-2017

3.6.1. Survival after CLL diagnosis compared to CLL population

The median time of follow-up for all 2631 CLL patients diagnosed between 2003–2012 was 6.7 years (Range, 0–15). Overall, 1311 (50%) of the patients were dead by 30 June 2018, and only six patients emigrated. Of the 77 patients with RS, 54 (70%) had died. No patient diagnosed with RS before 2010 was alive. Twelve (16%) patients were diagnosed with RS at the time of death.

Overall, the median duration of survival from CLL diagnosis was 1.7 years (95% CI, 0.34–2.3) for patients experiencing RS and 10.3 years (95% CI, 9.5–10.9) for the remaining patients ($p < 0.001$).

The actuarial 5-year survival rate was 13% (95% CI, 4–25) for patients with RS and 69% (95% CI, 67–71) for the remaining patients. The actuarial 10-year survival rate was 5% (95% CI, 1–11) for patients with RS and 50% (95% CI, 48–53) for the remaining patients.

In 1197 younger patients (age < 70) diagnosed with CLL between 2003–2012, the median survival from CLL diagnosis was 2.3 years (95%CI, 0.3–2.8) in 51 patients with RS while it was not reached (95%CI, 13.4-not reached) in 1146 remaining patients ($p < 0.0001$) (Fig. 2).

In 1434 older patients (age ≥70) diagnosed with CLL between 2003–2012, the median survival from CLL diagnosis was 0.8 years (95%CI 0.6–1.9) in 26 patients with RS and 5.6 years (95%CI, 5.1–5.9) in 1408 remaining patients ($p = 0.01$) (Fig. 2).

3.6.2. Survival after Richter syndrome between 2003-2017

Out of 77 patients with RS, 54 (70%) have died before the end of follow-up, and of these 12 were diagnosed at the time of death. Patients with RS were followed in median 17 months (Range; 1–102). The median survival from RS diagnosis was 27 months (95% CI, 9–88 months). Patients diagnosed with RS at the time of death were not included in the survival analysis.

The median survival from RS diagnosis was 27 months (95% CI, 13–33) for 56 patients with DLBCL and 9 months (95% CI, 4–88) for 11

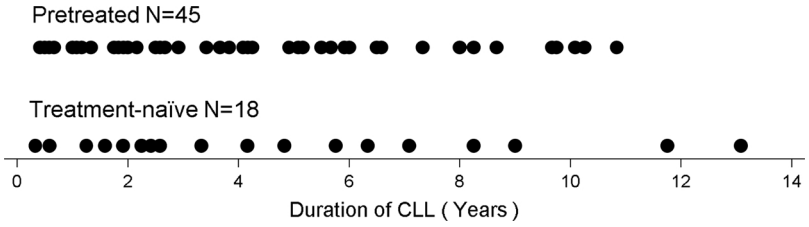


Fig. 1. Time from diagnosis of CLL to diagnosis of Richter syndrome in pretreated and treatment-naïve patients, 2003–2012. Patients diagnosed with Richter syndrome within 3 months after CLL diagnosis were excluded.

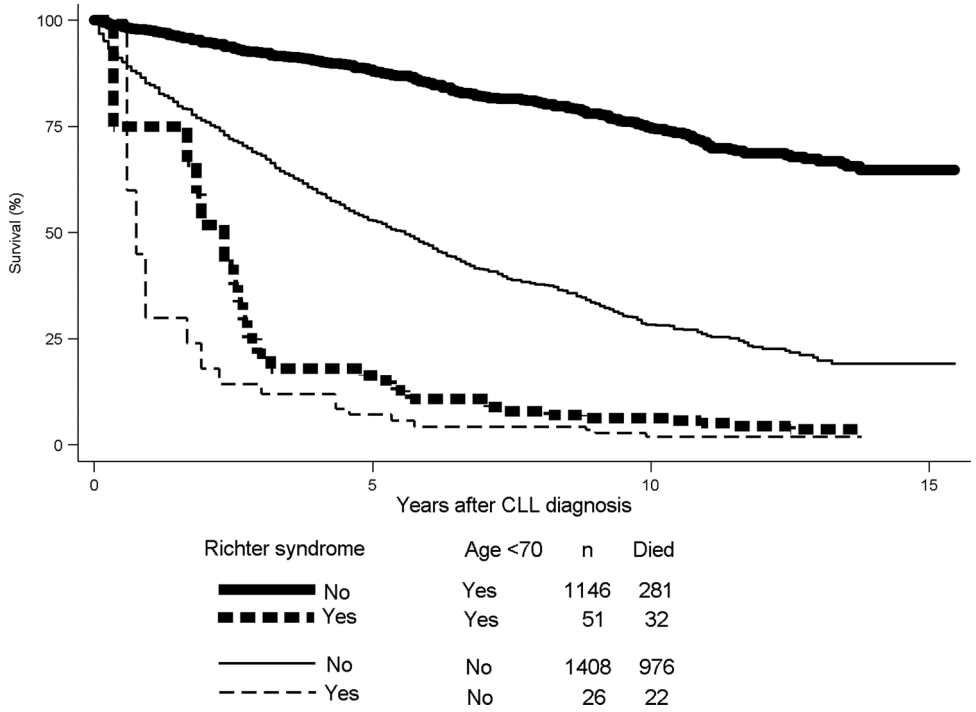


Fig. 2. Overall survival of patients with chronic lymphocytic leukemia diagnosed between 2003–2012 in patients < 70 and ≥70 years and a history of Richter syndrome.

patients with Hodgkin lymphoma.

The median survival from RS diagnosis was 14 months (95%CI, 8–29) in 38 pretreated patients and 77 months (95%CI, 13-not applicable) in 15 treatment naïve patients (p = 0.03).

4. Discussion

In this study from The Cancer Registry of Norway, we report on a doubling of the incidence of Richter syndrome in CLL patients diagnosed between 1993–2002 vs. 2003–2012 (1.9 vs. 4.7/1000 person-years). Based on the unselected nation-wide CLL population of this report, the prevalence of RS was 3% in patients diagnosed with CLL between 2003–2012. This corresponds to prevalence of 2.3% among newly diagnosed CLL patients seen at Mayo Clinic between 2000–2011 and a transformation rate of 0.5%/year [22]. The prevalence of RS in other retrospective studies varied from 1% to 10% and were mostly derived from institutional cohorts or follow-up of clinical studies and thus, the CLL populations studied were highly selected populations [12,23,24]. The main strength of our study is a completely unselected CLL cohort.

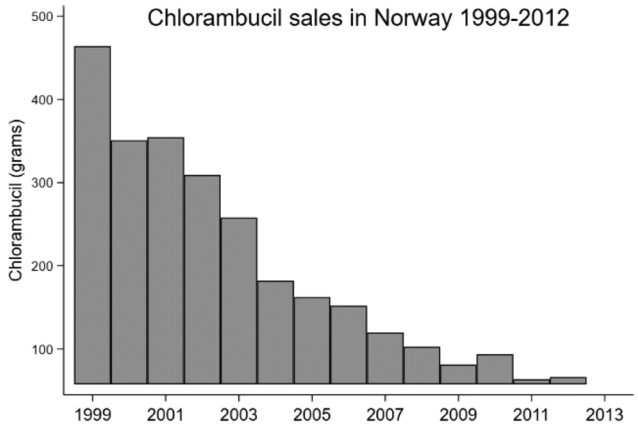
We screened the registry database broadly on possible lymphoma diagnoses in CLL patients and did not find any between 1953-1984. We suggest that this is a result of inadequate registration or the lack of vigilance for transformation among physicians. We revealed registration errors which occurred throughout the whole process of registration from the physicians reporting the diagnosis to the secretary plotting inn data to the registry database. The Cancer Registry is not responsible for the quality of diagnosis, and the study hematopathologist found several fault diagnoses registered both as CLL and Richter syndrome in the Cancer Registry. This clearly demonstrates some limitations of a" register-study".

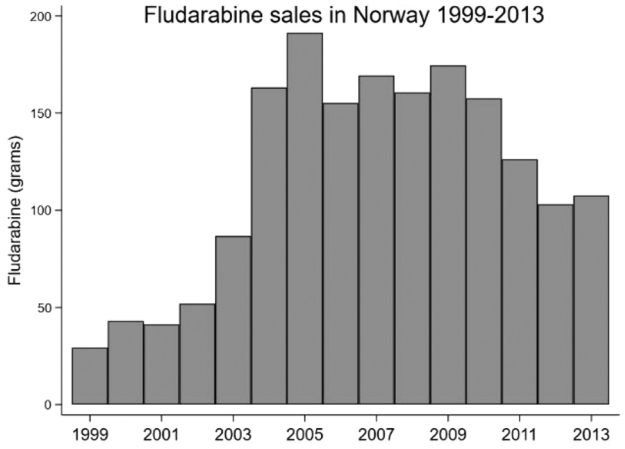
As a retrospective study, we are unable to assess possible causes of increased incidence of RS, such as whether the introduction of fludarabine and/or rituximab in CLL therapy contributes to the higher transformation rate. Firstly, we were unable to test for clonal relationship between CLL and lymphoma in this retrospective cohort. Secondly, we did not compare treatment history with a control group. The Cancer Registry did not store data on disease stage, risk factors and treatment. Individual hospitals all over Norway possess data on their patients and no common medical record database existed during the study period. Due to privacy and ethical constrains on the release of relevant individual-level information, extracting a control group was not feasible. However, this may be possible in the future in Norway when The National Quality Register for Lymphoma and Lymphoid Leukemia, which became statutory in 2013, is anchored among the treating physicians.

Interestingly, when we analyzed the aggregate-level information on fludarabin and chlorambucil sales in Norway between 1999–2013, available from the Norwegian Institute of Public Health, we found that the amount of fludarabine sold in Norway increased after 2003 while the amount of chlorambucil almost waned through 2000-ies (Figs. 3 and 4). As the main indication for fludarabine in Norway is CLL treatment, these results clearly indicate increased use of fludarabine for CLL patients between 2003–2012. On the other hand, 18 treatment-naïve patients in our RS cohort were diagnosed with CLL between 2003–2012, thus the improved registration coverage implemented by The Cancer Registry in 2003 plays probably a significant role in the incidence rise in the latest period.

In this report, the patients suffering from RS were diagnosed with CLL at younger age than the remaining patients (median age 65 vs. 71 years); and RS occurred early in the course of CLL both in treated and treatment-naïve patients. Half of the RS cases were diagnosed during the first two years of CLL diagnosis.

More than a quarter of RS patients had never received chemotherapy prior to transformation and half of these developed RS within 2 years of their CLL diagnosis. These findings are similar to reports from institutional series and disapprove a common misperception of RS as a late event in heavily pretreated CLL patients [12,13]. Furthermore, the pretreated patients in this cohort cannot be characterized as heavily pretreated, rather the opposite, 61% (38 of 45) of them received only one line of treatment and 24% [9] received two lines prior RS diagnosis was made. Considering previous suggestions of chemotherapy's contribution to RS development, our observation that RS is a rather early event in the course of CLL and that time to RS is equally





Figs. 3 and 4. Aggregate-level sales of fludarabine and chlorambucil in Norway, available from The Norwegian Institute of Public Health.

short in treatment naïve as in treated patients opposes this notion [18]. Interestingly, the treatment-naïve patients tended to be older at the time of CLL diagnosis than the treated patients were (median age 70 vs. 63 years, not significant), but they survived significantly longer after RS diagnosis (median survival 77 vs. 14 months).

A higher incidence of CLL in men compared to women has been consistently reported in most epidemiological studies, including in the Norwegian CLL population we studied in this report [21,25,26]. Moreover, in the CLL population we studied, we found lower 5-, 10- and 15- year survival in men compared to women in all age groups and study periods with the exception of an equal 5-year survival of men and women in patients younger than 60 years diagnosed between 2003–2012 [21]. This is in line with the report of Catovsky et al. in a patient population from four clinical trials [27]. We found an even more pronounced male predominance in CLL patients who developed RS (69% men) compared to the remaining CLL patients (58% men). Similarly, Parigh et al. report 78% vs. 65% male predominance (non-significant difference) in RS vs. "no RS" CLL patients from MD Anderson Cancer Center patients [13]. Tadmor et al. reports the proportion of men being 60% in DLBCL/RS and 70% in HL/RS patients in a multicenter study from Israel [12,14]. No gender proportion in patients developing RS was listed in studies on causes of kinase inhibitor discontinuation [5–7]. The only patient group with an equal gender proportion we found, were patients diagnosed with RS within the first 6 months of the CLL diagnosis. However, the number of patients (ten) is too low to draw any conclusions. Interestingly, we found a higher male predominance in RS/DLBCL patients compared to the remaining DLBCL patients in Norway (67% vs. 56%, $p = 0.0552$).

Both genetic and epigenetic studies have described gender differences in CLL patients. However, it is still unknown why men develop CLL and RS more often [27,28]. Understanding the reasons for incidence and survival differences among genders could provide clues both on etiology and management of CLL.

Here we confirmed previous research on RS and survival; RS clearly shortens survival of patients with CLL. The median survival of younger RS patients diagnosed with CLL between 2003–2012 was 2.3 years while the remaining younger CLL patients face life expectancy almost similar to the general population [21]. The younger age of RS patients in this cohort and the absence of heavily pretreated patients may be a result of "the real world" selection where clinicians omit biopsy in older and fragile CLL patients knowing that effective treatment is lacking.

Despite the limitations of this retrospective study, this is to our knowledge the first unselected, population-based epidemiological study on RS.

5. Conclusions

Our study shows that a well driven, population based cancer registry possesses useful information on a rare disease which is difficult to study in a prospective manner. Our report pays back for the clinicians' contribution and makes them aware of Richter syndrome early in the CLL course and even in treatment-naïve patients. Future collaboration between institutions and prospective biobanking of biological tissues from CLL patients should be established to gain more information on pathophysiology and treatment of RS.

Declaration of interest

None.

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

Authors' contributions

GET, TBJ, AL designed the study. AL analyzed the registry and patient data, drafted the manuscript. UR performed the histological examination. All authors read and approved the final manuscript

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References

[1] S.H. Swerdlow, E. Campo, S.A. Pileri, N.L. Harris, H. Stein, R. Siebert, et al., The 2016 revision of the World Health Organization classification of lymphoid neoplasms, Blood 127 (20) (2016) 2375–2390.

[2] J.R. Brown, P. Hillmen, S. O'Brien, J.C. Barrientos, N.M. Reddy, S.E. Coutre, et al., Extended follow-up and impact of high-risk prognostic factors from the phase 3

RESONATE study in patients with previously treated CLL/SLL, Leukemia (2017).
[3] P. Jain, P.A. Thompson, M. Keating, Z. Estrov, A. Ferrajoli, N. Jain, et al., Long-term outcomes for patients with chronic lymphocytic leukemia who discontinue ibrutinib, Cancer 123 (12) (2017) 2268–2273.
[4] M.A. Anderson, C. Tam, T.E. Lew, S. Juneja, M. Juneja, D. Westerman, et al., Clinicopathological features and outcomes of progression of CLL on the BCL2 inhibitor venetoclax, Blood 129 (25) (2017) 3362–3370.
[5] A.R. Mato, C. Nabhan, P.M. Barr, C.S. Ujjani, B.T. Hill, N. Lamanna, et al., Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience, Blood 128 (18) (2016) 2199–2205.
[6] K.J. Maddocks, A.S. Ruppert, G. Lozanski, N.A. Heerema, W. Zhao, L. Abruzzo, et al., Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia, JAMA Oncol. 1 (1) (2015) 80–87.
[7] S. O'Brien, R.R. Furman, S. Coutre, I.W. Flinn, J.A. Burger, K. Blum, et al., Single-agent ibrutinib in treatment-naive and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience, Blood 131 (17) (2018) 1910–1919.
[8] G. Fabbri, H. Khiabanian, A.B. Holmes, J. Wang, M. Messina, C.G. Mullighan, et al., Genetic lesions associated with chronic lymphocytic leukemia transformation to Richter syndrome, J. Exp. Med. 210 (11) (2013) 2273–2288.
[9] E. Chigrinova, A. Rinaldi, I. Kwee, D. Rossi, P.M. Rancoita, J.C. Strefford, et al., Two main genetic pathways lead to the transformation of chronic lymphocytic leukemia to Richter syndrome, Blood 122 (15) (2013) 2673–2682.
[10] D. Rossi, V. Spina, C. Deambrogi, S. Rasi, L. Laurenti, K. Stamatopoulos, et al., The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation, Blood 117 (12) (2011) 3391–3401.
[11] C. Vitale, A. Ferrajoli, Richter syndrome in chronic lymphocytic leukemia, Curr. Hematol. Malig. Rep. 11 (1) (2016) 43–51.
[12] T. Tadmor, L. Shvidel, O. Bairey, N. Goldschmidt, R. Ruchlemer, R. Fineman, et al., Richter's transformation to diffuse large B-cell lymphoma: a retrospective study reporting clinical data, outcome and the benefit of adding rituximab to chemotherapy, from the Israeli CLL Study Group, Am. J. Hematol. (2014).
[13] S.A. Parikh, K.G. Rabe, T.G. Call, C.S. Zent, T.M. Habermann, W. Ding, et al., Diffuse large B-cell lymphoma (Richter syndrome) in patients with chronic lymphocytic leukaemia (CLL): a cohort study of newly diagnosed patients, Br. J. Haematol. 162 (6) (2013) 774–782.
[14] T. Tadmor, L. Shvidel, N. Goldschmidt, R. Ruchlemer, R. Fineman, O. Bairey, et al., Hodgkin's variant of Richter transformation in chronic lymphocytic leukemia; a retrospective study from the Israeli CLL study group, Anticancer Res. 34 (2) (2014) 785–790.
[15] X.S. Puente, S. Bea, R. Valdes-Mas, N. Villamor, J. Gutierrez-Abril, J.I. Martin-Subero, et al., Non-coding recurrent mutations in chronic lymphocytic leukaemia, Nature 526 (7574) (2015) 519–524.
[16] D.A. Landau, E. Tausch, A.N. Taylor-Weiner, C. Stewart, J.G. Reiter, J. Bahlo, et al., Mutations driving CLL and their evolution in progression and relapse, Nature 526 (7574) (2015) 525–530.
[17] L. Fan, L. Wang, R. Zhang, C. Fang, D.X. Zhu, Y.H. Wang, et al., Richter transformation in 16 of 149 Chinese patients with chronic lymphocytic leukemia, Leuk. Lymphoma 53 (9) (2012) 1749–1756.
[18] D. Rossi, Richter syndrome and fludarabine: a controversial relationship, Leuk. Lymphoma 54 (2) (2013) 213–214.
[19] D. Rossi, V. Spina, R. Bomben, S. Rasi, M. Dal-Bo, A. Bruscaggin, et al., Association between molecular lesions and specific B-cell receptor subsets in chronic lymphocytic leukemia, Blood 121 (24) (2013) 4902–4905.
[20] B. Bockorny, I. Codreanu, C.A. Dasanu, Hodgkin lymphoma as Richter transformation in chronic lymphocytic leukaemia: a retrospective analysis of world literature, Br. J. Haematol. 156 (1) (2012) 50–66.
[21] A. Lenartova, T.B. Johannesen, G.E. Tjonnfjord, National trends in incidence and survival of chronic lymphocytic leukemia in Norway for 1953-2012: a systematic analysis of population-based data, Cancer Med. 5 (12) (2016) 3588–3595.
[22] S.A. Parikh, N.E. Kay, T.D. Shanafelt, How we treat Richter syndrome, Blood 123 (11) (2014) 1647–1657.
[23] A.M. Tsimberidou, S. O'Brien, I. Khouri, F.J. Giles, H.M. Kantarjian, R. Champlin, et al., Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation, J. Clin. Oncol. 24 (15) (2006) 2343–2351.
[24] D. Rossi, M. Cerri, D. Capello, C. Deambrogi, F.M. Rossi, A. Zucchetto, et al., Biological and clinical risk factors of chronic lymphocytic leukaemia transformation to Richter syndrome, Br. J. Haematol. 142 (2) (2008) 202–215.
[25] H. Brenner, A. Gondos, D. Pulte, Trends in long-term survival of patients with chronic lymphocytic leukemia from the 1980s to the early 21st century, Blood 111 (10) (2008) 4916–4921.
[26] G.M. Dores, W.F. Anderson, R.E. Curtis, O. Landgren, E. Ostroumova, E.C. Bluhm, et al., Chronic lymphocytic leukaemia and small lymphocytic lymphoma: overview of the descriptive epidemiology, Br. J. Haematol. 139 (5) (2007) 809–819.
[27] D. Catovsky, R. Wade, M. Else, The clinical significance of patients' sex in chronic lymphocytic leukemia, Haematologica 99 (6) (2014) 1088–1094.
[28] S. Lin, Y. Liu, L.R. Goldin, C. Lyu, X. Kong, Y. Zhang, et al., Sex-related DNA methylation differences in B cell chronic lymphocytic leukemia, Biol. Sex Differ. 10 (1) (2019) 2.