BACKGROUND

More than 20 000 patients are diagnosed with chronic lymphocytic leukemia (CLL) in USA each year.\(^1\) The annual incidence of CLL is approximately 320 cases in Norway, in a population of 5.3 million.\(^2\)

The overall 5-year survival reached 85% in USA (2009-2015) and 79% in Norway (2003-2012), and in USA, estimated 178.206 patients lived with CLL in 2016.\(^3\)

Patients with CLL face substantial morbidity due to other causes than CLL: for example, infections, autoimmune diseases, and second solid and hematological malignancies.\(^4\) Little is known about the epidemiology of second hematological malignancies (SHM) in patients with chronic lymphocytic leukemia (CLL) not participating in clinical trials.\(^5\)\(^-\)\(^9\) Prevalence of t-MDS and t-AML in chemotherapy/chemoimmunotherapy-treated patients with CLL is about 1%-8% in CLL populations reported from tertiary referral institutions or

Abstract

Objective: Chronic lymphocytic leukemia (CLL) treatment has changed dramatically, and landscape of second hematologic malignancies (SHM) evolves in the new era of targeted therapy. No data were available about the real-world burden of SHM.

Methods: All 2631 patients with CLL in the Cancer registry of Norway registered 2003-2012 were included.

Results: After median follow-up of 6.6 years, 103 patients (4%) developed SHM. Diffuse large B-cell lymphoma (DLBCL) was most common (n = 65; 63%), Median survival was 9.3 years (95% CI: 8.9-9.8) in non-SHM patients and 1.7 years in DLBCL, 0.8 years in Hodgkin lymphoma (n = 12), and 2.8 years in myeloid neoplasia (n = 15; 95% CI: 0.3-2.6, 0.6-2.9, and 0.4-5.3, respectively; \(P < .001\)). Outcomes were poorest for SHM patients treated for CLL (HR 2.76, 95% CI 1.4-5.5, \(P = 0.003\)). A higher proportion of men and younger age were found in SHM patients (median age 66 vs 72 years in non-SHM; \(P < .001\); men 68% vs 57%, \(P = .03\)). Myeloid neoplasia was rare (incidence rate 1/1000 person-years; 95% CI: 0.6-1.5) and tended to occur later than DLBCL in patients treated for CLL (median time from CLL to SHM 62 vs 45 months; \(P = .09\)).

Conclusions: SHM and especially myeloid malignancies were rare in chemoimmunotherapy era.

KEYWORDS

chemoimmunotherapy, chronic lymphocytic leukemia, epidemiology, Nation-wide cancer registry, real-world, second hematologic malignancy, therapy-related myeloid neoplasia
clinical trials with median age between 60 and 65 years, for example, about 10 years younger than the "real-world" CLL population.\textsuperscript{10} Reports on a general unselected CLL population are based on cancer registries.\textsuperscript{11,12} Among 15,915 patients with CLL surviving at least 1 year after diagnosis of CLL registered in 11 SEER registries in USA between 1992 and 2006, only 13 cases of acute non-lymphoblastic leukemia were registered (mean person-years at risk 4.3).\textsuperscript{5}

Treatment of CLL is about to change dramatically; from therapy based on cytotoxic drugs, to therapy based on drugs targeting signaling pathways, and importantly, free for cytotoxic drugs. DNA damage induced by cytotoxic drugs is an established factor in the pathogenesis of secondary myeloid malignancies in solid cancer.\textsuperscript{13,14} The new targeted agents seem to increase genomic instability by other mechanisms, which are of concern, as patients are supposed to receive targeted agents for years. Thus, whether secondary myeloid neoplasms in CLL will be reduced with diminishing use of cytotoxic drugs or the landscape of entities will change should be kept an eye on.

Both pretreated and treatment-naive patients with CLL develop myeloid neoplasia. Myeloid neoplasms in pretreated patients with CLL are defined as late complication of cytotoxic chemotherapy or radiotherapy by WHO Classification of Hematologic malignancies and include therapy-related myeloid neoplasms (t-MN); for example, therapy-related acute myeloid leukemia (t-AML), myelodysplastic syndrome (t-MDS), and myelodysplastic/myeloproliferative neoplasms (t-MDS/MPN).

Myeloid neoplasms in previously untreated patients with CLL are referred to as second myeloid neoplasms (s-MN), for example, second MDS (s-MDS) and second AML (s-AML). The term secondary myeloid neoplasm usually refers to both therapy-related and second myeloid neoplasms.

Outcomes of patients with CLL acquiring myeloid malignancy are very poor.\textsuperscript{8,15} Reports suggest biological and outcome differences between therapy-related myeloid neoplasm patients and second myeloid neoplasms.\textsuperscript{15}

In this article, we focus on epidemiological patterns of second hematological malignancies, with focus on myeloid malignancies in a national cohort of patients with CLL registered between 2003 and 2012 at the Cancer Registry of Norway. As a result of nation-wide CLL registration since 1953, the trends on CLL epidemiology are available for 50 years prior to the studied period.\textsuperscript{3} In addition, detailed epidemiology of Richter syndrome (diffuse large B-cell lymphoma, DLBCL, and Hodgkin lymphoma, HL) in this particular cohort has been described previously and here we update survival data.\textsuperscript{16}

2 | METHODS

2.1 | Study population

In this observational, population-based, retrospective cohort study of all 2631 patients with CLL registered at the Cancer Registry of Norway between 2003 and 2012, we identified 770 patients with notification of additional malignancies in blood, bone marrow, or lymphoid tissue by December 31, 2017. Reporting to the registry is mandatory, and the registry records all laboratory findings of malignancy to ensure completeness, and a single patient record includes repeated notifications. Thus, of 770 patients identified, pathological and clinical reports stated a new diagnostic entity in 103 patients and confirmed CLL as the only hematological malignancy in the remaining patients.

The date of CLL diagnosis was available from the Cancer Registry. Survival data were available from the Norwegian Registry of Cause of Death and were updated by December 31, 2018. Prior CLL treatment, time and characteristics of MDS and acute leukemia were registered from patients’ medical records and clinical reports to the registry. We received data on nation-wide MDS 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 | Statistical analysis

Patients were followed from the date of CLL or SHM diagnosis to the date of SHM (by December 31, 2017) time of death, date of emigration or last follow-up (by December 31, 2018), median 6.6 years (Range: 0.003-15.5) from CLL to SHM occurrence, and 7.1 years from CLL and 1.6 years from SHM diagnosis to death or end of follow-up (Range: 0.08-16 and 0.1-15.6). The reversed Kaplan-Meier method was used to calculate follow-up time. Seven patients emigrated (all non-SHM patients).

Incidence rates report number of documented cases divided by total person-years of follow-up.

The Kaplan-Meier method, corrected for immortal bias using "stsplits" command, was used to calculate survival. Age- and sex-stratified log-rank test was used in comparative survival analysis in groups larger than 20 patients, and Mann-Whitney-Wilcoxon rank-sum test was used in smaller groups. Cox proportional hazard ratio was calculated by Cox regression analysis method.

Age was compared using Student’s t test. The proportion of males and females were compared using Pearson’s chi-square test. All tests were two-sided. Statistical analyses were performed using STATA version 15.1 (StataCorp).
3 | RESULTS

3.1 | Study population

Among 2631 patients with CLL, 103 (3.9%) were registered with a second hematologic malignancy (SHM) after a median follow-up of 6.6 years (Table 1). The proportion of men was 68% among SHM patients and 57% among the remaining patients with CLL (P = .033). Median age at CLL diagnosis was 66 years in SHM patients and 72 years in the remaining patients (P < .001). Median age was lowest in patients with therapy-related myeloid neoplasia (t-MN; 60 years).

3.2 | Risk of second hematologic malignancy among patients with CLL

Incidence rates of second hematologic malignancy in the CLL population are depicted in Table 1. Lymphoid neoplasia was diagnosed in 88 of 103 (85%) patients, and DLBCL was by far the most common SHM (65 of 103, 63%). Time elapsed between CLL and SHM

| TABLE 1 | Second hematologic malignancy in CLL patients registered at Cancer Registry of Norway 2003-2012 |
|---|---|---|---|---|
| No. of patients (%) | Incidence/1000 py (95% CI) | Survival from CLL diagnosis (95% CI) | Log-rank test, P-value |
| All CLL patients | 2631 (100) | 9.1 y (8.6-9.5) |  |
| Second hematologic malignancy, all |  |
| Yes | 103 (4) | 6.4 (5.2-7.7) | 2.3 y (0.8-3.2) | <.001<sup>a</sup> |
| No | 2528 (96) | 9.3 y (8.9-9.8) |  |
| Second hematologic malignancy, subgroups |  |
| Diffuse large B-cell lymphoma |  |
| All patients | 65 (2.5) | 4.0 (3.1-5.1) | 1.7 y (0.3-2.6) | <.001 |
| Treated for CLL | 39 | 2.4 (1.7-3.3) |  |
| Treatment-naïve | 20 | 1.2 (0.8-1.9) |  |
| Unknown | 6 |  |
| Myeloid neoplasia |  |
| All patients | 15 (0.6) | 0.92 (0.6-1.5) | 2.8 y (0.4-5.3) | <.001 |
| Treated for CLL | 12 | 0.73 (0.4-1.3) |  |
| Treatment-naïve | 3 | 0.18 (0.06-0.6) |  |
| MDS | 12 | 0.73 (0.4-1.3) |  |
| Treated for CLL | 9 | 0.55 (0.3-1.1) |  |
| Treatment-naïve | 3 | 0.18 (0.06-0.6) |  |
| AML | 3 | 0.18 (0.06-0.6) |  |
| Treated for CLL | 3 | 0.18 (0.06-0.6) |  |
| Hodgkin lymphoma |  |
| All patients | 12 (0.5) | 0.7 (0.4-1.3) | 0.8 y (0.6-2.9) | <.001 |
| Treated for CLL | 7 | 0.4 (0.2-0.9) |  |
| Treatment-naïve | 4 | 0.3 (0.09-0.7) |  |
| Unknown | 1 |  |
| Splenic marginal zone lymphoma |  |
| All patients | 8 (0.3) | 0.5 (0.3-1.0) | 5.8 y (4.9-NC) | .912 |
| Mantel cell lymphoma |  |
| All patients | 2 (0.08) | 0.1 (0.03-0.5) | 4.8 y (NC-4.8) | .212 |
| Burkitt lymphoma |  |
| All patients | 1 (0.04) | 0.06 (0.0-0.4) | Alive | |
| T-cell prolymphocytic leukemia |  |
| All patients | 1 (0.04) | 0.06 (0.0-0.4) | Diagnosed at time of death | |

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndrome; NC, not calculable; py, person-years.

<sup>a</sup>Tested value.
diagnosis was less than 4 months in 17 (17%) patients and a median of 4 years (Range: 0.4-13) in the remaining patients. Time from CLL diagnosis to t-MN was 62 months (Range: 29-158) and to diffuse large B-cell lymphoma 45 months (Range: 7-130, Wilcoxon rank-sum-Mann-Whitney test \( P = .087 \)). (Figure 1).

### 3.3 Effect of second hematologic malignancy on CLL survival

Of 2528 non-SHM patients, 1401 (55%) died. Of 103 patients with SHM, 80 (82%) died. Patients with DLBCL, myeloid malignancy, and Hodgkin lymphoma survived shorter after CLL diagnosis than remaining patients with CLL, while survival of patients developing marginal zone lymphoma did not differ significantly (Table 1).

#### 3.4 Survival after second hematological malignancy

Eighteen of 65 (28%) patients with DLBCL, 2 of 12 (17%) with Hodgkin lymphoma, 2 of 8 (25%) with marginal zone lymphoma, and one of three (33%) with second myelodysplastic syndrome were alive by the end of the study.

Figure 2 illustrates length of survival from second hematological malignancy. The patient with Burkitt lymphoma died 11.5 years after diagnosis. Two patients with mantel cell lymphoma died after 4.8 and 6.4 years. Six patients with marginal zone lymphoma died after a median of 5.2 years (Range: 2.25-7.7). Ten patients with Hodgkin lymphoma died after a median of 7 months (Range: 0-88) and patients with DLBCL after median 8 months (Range: 0-88). The patient with T-prolymphocytic leukemia was diagnosed at the time of death.
3.5 Pretreated vs not treated patients with aggressive second hematologic malignancy

Considering patients with worse outcomes, for example, DLBCL, Hodgkin lymphoma, MDS, or AML, those who received CLL treatment were younger and survived shorter than those who did not receive treatment prior SHM diagnosis (Figure 3). The treatment history was known in 84/91 (92%) patients. Median age in 57 pretreated patients was 63 years vs 67 years in 27 treatment-naive patients (t test \( P < .001 \)). Median survival after SHM was 0.8 in treated and 6.4 years in treatment-naive patients (95% CI: 0.7-1.6 vs 1.1-noncalculable; age- and sex-stratified log-rank test: \( P = .0016 \); Cox proportional hazard ratio 2.76, 95% CI: 1.4-5.5, \( P = .003 \). 11 patients died at the time of SHM diagnosis).

3.6 Myelodysplastic syndrome in patients with CLL

Among 2631 patients with CLL, 12 (0.5%) patients were registered with MDS. In Norway, 2160 patients ≥40 years old were registered with MDS between 2003 and 2017; thus, 12 patients with CLL/MDS constitute only 0.6% of the total disease burden.

MDS was diagnosed prior to CLL treatment in three patients (s-MDS) and after CLL treatment in nine patients (t-MDS).

All three patients with s-MDS were men diagnosed concurrently with MDS and CLL at a median age of 67 years (Range: 62-74). At the end of the follow-up, one patient was alive 13 years after MDS diagnosis and two patients died 0.5 and 11 years after MDS diagnosis.

Six of nine pretreated patients (t-MDS) were men. Median age was 60 years (Range: 51-75) in 9 t-MDS patients and 72 years in remaining patients with CLL (\( P < .001 \)).

Of nine t-MDS patients, eight patients were diagnosed with CLL at an advanced stage (Binet B and C). Median time between CLL and MDS diagnoses was 57 months (Range: 29-158). MDS evolved to AML in five patients (all t-MDS). Patients survived at a median of nine months after MDS diagnosis (Range: 2-25). All patients were dead by the end of the study.

3.7 Treatment history in therapy-related myeloid malignancy

All three AML patients were treated for CLL prior to AML diagnosis, and one had DLBCL prior to AML diagnosis. Thus, summarized, 12 patients who developed therapy-related myeloid neoplasia received in median 1.5 treatment lines (Range: 1-5). Fludarabine was administered to 11 (92%) patients; combined with cyclophosphamide and rituximab (FCR) in 10. Three patients received bendamustine with rituximab, two chlorambucil and none pathway inhibitors, and none had been registered with other malignancies.

Four patients received only one line of CLL treatment. They received fludarabine, cyclophosphamide, and rituximab for Binet stage B or C disease and achieved partial or complete remission. MDS developed in median of 4 years after treatment (Range: 2-5.2 years).

4 DISCUSSION

In this population-based retrospective study, we found a second hematologic malignancy in 4% of all patients with CLL diagnosed in Norway between 2003 and 2012. Lymphoid malignancies occurred at a sixfold higher rate than myeloid. The same tendency toward younger age and dismal survival characterized these subpopulations. Myeloid neoplasia was rarely diagnosed and almost never in elderly patients.

Incidence of second myeloid malignancy was very low compared to reports from long-term follow-up of clinical trials. Even
though the studied population had a median age of 72 years, therapy-related myeloid neoplasm occurred as a late event in patients diagnosed with CLL 10 years younger than median. The cohort in this study included all Norwegian patients, but because we did not have data on treatment of the entire cohort, direct comparison with cohorts from clinical trials is not possible. We have previously reported on a subset of the population studied here, for example, all Norwegian patients with CLL diagnosed between 2007 and 2010, with a coverage of 61% and found that of newly diagnosed patients, 80% were diagnosed in Binet A stage and did not fulfill criteria for initiation of CLL treatment.\(^3\)

The absence of myeloid neoplasia in elderly patients with CLL in real-world setting was striking. An important factor can be shorter CLL survival in elderly patients with CLL; thus, fewer survive long enough to develop therapy-related myeloid neoplasm. Median observed survival in this studied cohort was 11 years in age-group 60-69 years, 7 years in age-group 70-79, and 3 years in age-group 80 and older.\(^3\)

Cytopenia is a common problem in patients with CLL, including the elderly. We do not have any evidence suggesting the elderly being spared for second myeloid malignancy. On the contrary, the incidence of myeloid malignancies increases with age in the general population.\(^19,20\) To diagnose MDS, suspicion of MDS and proper diagnostic workup is necessary. Outcomes of s-MDS are poor and in elderly, few, if any therapeutic options existed. Thus, a well-considered nihilism may be an explanation for the absence of MDS being diagnosed in the elderly patients with CLL. In the real-life setting, cytopenia in a patient with CLL is often considered the sign of CLL progression or the side effect of treatment. Bone marrow biopsy is not routinely performed in patients with CLL outside clinical trials, and accordingly, a MDS as the course of cytopenia can be missed. The rate of missing MDS diagnoses is unknown as the cancer registry is not responsible for diagnosis accuracy, but under-reporting truly is an important reason of unexpectedly low incidence of myeloid neoplasias in the era of chemoimmunotherapy in this study.

In the studied period, chlorambucil, bendamustine, and rituximab were drugs of choice where as FCR was not recommended in elderly patients, while most patients with t-MN identified, were treated with FCR regimens. Occurrence of t-MN after chlorambucil and bendamustine treatment reported in clinical trials is very low and substantially lower than after fludarabine-based regimens.\(^21-24\) However, since the t-MN occur several years after CLL treatment, the length of follow-up plays a substantial role in reporting incidence rates of t-MN. The long follow-up is a strength of our study.

SHM occurred both in treatment-naïve and pretreated patients with CLL. Patients treated for CLL prior to diagnosis of myeloid neoplasm diffuse large B-cell lymphoma, and Hodgkin lymphoma were more often men, were younger, and survived shorter than patients not treated for CLL with SHM. Why these populations differ is not clear. Because of the retrospective character of this study, a selection bias/surveillance bias was impossible to control for and may play role in these findings. Our study cannot answer whether this difference is due to biological characteristics of their CLL or whether CLL treatment plays a role in shorter survival of CLL-treated patients when they acquire SHM. However, outcomes are known to be worse in t-MDS when compared to primary MDS.\(^25,26\)

Interestingly, we confirmed that MN tends to occur later than DLBCL in treated patients, suggesting different pathogenesis.\(^15,27\)

Comparative studies of patients developing MN vs DLBCL could contribute to clarify pathogenesis in these rare, but devastating entities.

Despite the limitations of this retrospective study, a real-world burden of therapy-related myeloid neoplasia was very low in the study period in which chemoimmunotherapy was the cornerstone of CLL treatment in Norway.

The main strength of this study is the high grade of completeness on a nation-wide unselected CLL cohort followed for a long time and thus mirrors the real burden of the second hematologic malignancies. Treatment of CLL is about to change dramatically; from therapy based on cytotoxic drugs, to therapy based on drugs targeting signaling pathways, and, importantly, free for cytotoxic drugs. DNA damage induced by cytotoxic drugs is an established factor in the pathogenesis of secondary myeloid malignancies in solid cancer survivors. Myeloid neoplasia in patients with CLL was uncommon in the era of cytotoxic drugs, for example, the era of chemoimmunotherapy.\(^1\)

The new targeted agents seem to increase genomic instability by other mechanisms, which are of concern, as patients are supposed to receive targeted agents for years.\(^17,18\) Prolonged survival and long-term immunosuppression due to both CLL and targeted therapy may expand the population with higher risk of secondary malignancies.\(^28,29\) This may be particularly relevant for an elderly population in which chemoimmunotherapy is less beneficial.\(^30,31\) Thus, the epidemiology of secondary malignancies with targeted therapy can be influenced by other mechanisms in contrast with chemotherapy that directly leads to DNA damage.

5 | CONCLUSIONS

Second hematologic malignancy was a rare event in patients with CLL, and lymphoid malignancy was diagnosed at a sixfold higher rate than myeloid. Despite younger age of patients with second hematologic malignancy, CLL survival was significantly shortened. A well-driven cancer registry provides opportunity for future surveillance of a rare entity.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.
AUTHOR CONTRIBUTIONS
AL gathered, analyzed, and interpreted data and wrote the manuscript. TBJ and GET initialized the study, contributed to the manuscript, and read and approved the final manuscript.

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

CONSENT TO PARTICIPATE
The committee decided that consent to participate was not necessary due to importance of the study for society and high mortality rate of participants.

DATA AVAILABILITY STATEMENT
The datasets used during the study are available from the corresponding author on reasonable request.

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