

Observational evidence from patients diagnosed with chronic lymphocytic leukaemia (CLL) in Finland between 2005-2015 show improved survival over time

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Abstract

Objectives: We aimed to describe treatment patterns of chronic lymphocytic leukaemia (CLL) patients in routine practice settings, compare overall survival and time-to-next-treatment among patients treated in different time periods (2005-2008, 2009-2013, 2014-2015), and explore associated factors.

Methods: This retrospective cohort study included adult CLL patients from the Finnish Hematology Registry.

Results: In total, 124 and 64 CLL patients received first- and second-line treatments, respectively. The use of first- and second-line treatments with bendamustine-rituximab (BR) increased, while chlorambucil-based treatments decreased over time. Patients treated in more recent years showed a trend towards longer first- and second-line survival. A trend towards inferior overall survival was detected in first- and second-line treatment with B/BR. First-line time-to-next-treatment was longer for patients treated in the later years towards 2015, while second-line time-to-next-treatment did not improve over time.

Conclusions: This study identified that improved treatment outcomes over time were likely influenced by patient characteristics and treatments, but also through other factors unexplored in this study. Hence, further research on the factors influencing patients' survival over time is needed. In particular, research on using B/BR in clinical practice is warranted.

KEYWORDS

chemoimmunotherapy, chronic lymphocytic leukaemia, epidemiology, Finland, registry, survival

1 | INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia reported in most European and North American countries.¹ It is a lymphoproliferative disorder characterised by the gradual

accumulation of morphologically mature lymphocytes. Although CLL remains incurable, survival rates have improved over time,²⁻⁴ to approximately 80% 5-year survival in Europe and North America.^{2,3} In Finland, approximately 2,600 individuals live with CLL, with approximately 350 diagnosed annually.⁵ In routine Finnish clinical

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practice, treatment patterns and outcomes of patients with CLL have not been previously assessed.

Fludarabine-based combination therapy is the cornerstone of first-line treatment for physically fit patients with CLL, being previously used exclusively in combination with cyclophosphamide (fludarabine-cyclophosphamide, FC),⁶ and today recommended in combination with both cyclophosphamide and the monoclonal anti-CD20 antibody rituximab (fludarabine-cyclophosphamide-rituximab, FCR).^{7,8} Over time, the choice of first-line treatment in patients unfit for FC/FCR has shifted from chlorambucil or cyclophosphamide⁹ to bendamustine combined with rituximab (BR) or chlorambucil combined with a monoclonal anti-CD20 antibody. Second-line treatment with monoclonal antibodies has also become recommended.^{7,8} Since 2014, B-cell receptor (BCR) inhibitors have been used as targeted treatments for certain patients with CLL, at first and later lines.^{7,8} Over time, Finnish treatment guidelines¹⁰ have aligned with the international recommendations.^{7,8}

Observational data from routine clinical practice enable investigation into how recommended treatment guidelines are utilised and helps in assessing the effects of therapies more broadly than in randomized controlled trials.¹¹ Prior studies with real-world data have reported the overall survival (OS) from CLL diagnosis improving over time.^{3,12-14} However, a population-based study in Sweden¹⁵ did not find significant improvement over time in second-line outcomes, despite the increased use of novel therapies, including chemoimmunotherapy. Temporal trends have been studied until 2013,^{2,3,12-15} after which BR became more established as a standard first-line option for elderly patients. Furthermore, these investigations in time trends using real-world data did not adjust for differing clinical characteristics and treatments,^{2,3,12-15} leaving the influence of these factors on treatment outcomes unknown.

The objectives of this study were to describe treatment patterns for patients with CLL in first- and second-line routine practice settings at the Helsinki University Hospital, Finland, to compare the OS and time-to-next-treatment (TTNT) between patients treated in different time periods (2005-2008, 2009-2013, 2014-2015), and to explore factors associated with OS and TTNT.

2 | MATERIALS AND METHODS

This was an observational retrospective cohort study using existing register data from the Finnish Hematology Registry (FHR).¹⁶ The FHR was created to collect routine clinical practice outcomes in patients with CLL and other haematological malignancies, enabled by Finland's centralised nationwide healthcare system for reliable patient identification and comprehensive follow-up.

From the FHR, adult patients (≥ 18 years) diagnosed with CLL were included in this study if they received one or more treatment lines during 2005-2015 at the Helsinki University Hospital, Finland, a hospital region accounting for 26% of the national CLL incidence.⁵ Each included patient was followed-up from the date of first-line CLL treatment initiation (1st January 2005 - 31st December 2015), until the end of follow-up, defined as the end of study period (31st

December 2015) or death, whichever came first. For this study, patients were divided into three mutually exclusive groups based on each patient's time of initiating the first- and subsequently second-line treatment: 2005-2008, 2009-2013 or 2014-2015, referred to as the *early*, *middle*, or *late* time periods, respectively.

All study variables were extracted as available from the FHR, including the following patient characteristics at the initiation of first-line and second-line treatments: age, gender, Binet stage, cytogenetic lesions using the fluorescence in situ hybridization (FISH) test, immunoglobulin heavy chain variable (IgHV) mutational status, comorbidity index, blood leukocyte count, year of CLL diagnosis, and time to progression (ie time between first-line end and second-line treatment initiation, for second-line only). The comorbidity index was derived according to Charlson,¹⁷ as applicable with FHR data (Appendix S1).

Treatment regimens at first- and second-line were categorised into the following mutually exclusive categories:

- Fludarabine-cyclophosphamide or fludarabine-cyclophosphamide-rituximab (FC/FCR)
- Bendamustine or bendamustine-rituximab (B/BR)
- Regimens other than FC/FCR or B/BR were, further divided into:

Chlorambucil without monoclonal antibody

Monoclonal antibody-based therapies alone or in combination (other than FCR or BR). Among them, chlorambucil-based therapies were described separately

Other treatments, including therapies with glucocorticoids, cyclophosphamide or fludarabine, excluding therapies in any of the other categories

BCR inhibitors were not used as first- or second-line treatments during the study period and were seldom used in subsequent treatment lines for this population (4 patients), as idelalisib-rituximab was reimbursed in Finland in October 2015, and ibrutinib was available only with special permission during the study period.

The OS and TTNT were assessed from the initiation of first- or second-line treatments. Patient characteristics and treatment regimens at first- and second-line were reported descriptively for all included patients at first- and second-line, and stratified by the treatment initiation period. The outcomes were explored with the Kaplan-Meier estimator and differences in survival distributions were compared using the log-rank test. Outcomes between the time periods were further compared using a multivariate Cox model adjusted for patient characteristics at the start of first- or second-line treatment and the treatment regimen given within the treatment line (FC/FCR, B/BR, or other). In the Cox models, factors associated with OS and TTNT were also explored, and the analysis of second-line treatment was adjusted for the first-line treatment. The adjusted Cox model results were presented as hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs). Missing data for variables were described and used without imputation in the analyses (see Appendix S1 for more details). R software 3.1.1 was used.

The study was performed in accordance with the declaration of Helsinki and in compliance with national laws. Ethical approval was

**TABLE 1** Patient characteristics at initiation and treatment regimens of first and second treatment line, by the treatment line initiation period

Patient characteristic	First-line treatment initiation period				Second-line treatment initiation period			
	Early: 2005-2008 (N = 32)	Middle: 2009-2013 (N = 77)	Late: 2014-2015 (N = 15)	In total: 2005-2015 (N = 124)	Early: 2006 ^b -2008 (N = 6)	Middle: 2009-2013 (N = 41)	Late: 2014-2015 (N = 17)	In total: 2006 ^b -2015 (N = 64)
Age (y)								
Median (range)	66 (39-86)	66 (27-86)	69 (55-82)	66 (27-86)	71 (61-84)	71 (27-84)	69 (58-89)	71 (27-89)
18-64, n (%)	14 (44)	35 (45)	3 (20)	52 (42)	1 (17)	13 (32)	4 (24)	18 (28)
65-74, n (%)	13 (41)	33 (43)	11 (73)	57 (46)	3 (50)	15 (37)	8 (47)	26 (41)
≥75, n (%)	5 (16)	9 (12)	1 (7)	15 (12)	2 (33)	13 (32)	5 (29)	20 (31)
Gender male, n (%)	24 (75)	54 (70)	7 (47)	85 (69)	5 (83)	29 (71)	13 (77)	47 (73)
Binet stage								
A, n (%)	15 (47)	30 (39)	7 (47)	52 (42)	2 (33)	19 (46)	5 (29)	26 (41)
B, n (%)	5 (16)	19 (25)	2 (13)	26 (21)	0 (0)	3 (7)	2 (11)	5 (8)
C, n (%)	11 (34)	28 (36)	6 (40)	45 (36)	4 (67)	19 (46)	10 (59)	33 (52)
Missing, n (%)	1 (3)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Cytogenetic lesions (FISH)								
Investigated, n (%)	11 (34)	56 (73)	13 (87)	80 (65)	3 (50)	25 (61)	15 (88)	43 (67)
del(13q) positive, n (%)	6 (19)	38 (49)	7 (47)	51 (41)	3 (50)	19 (46)	12 (71)	34 (53)
del(11q) or del(17p) positive, n (%)	2 (6)	14 (18)	1 (7)	17 (14)	2 (33)	12 (29)	2 (12)	16 (25)
Trisomy 12 positive, n (%)	2 (6)	7 (9)	3 (20)	12 (10)	0 (0)	2 (5)	3 (18)	5 (8)
IgHV mutation								
Mutated, n (%)	1 (3)	6 (8)	3 (20)	10 (8)	0 (0)	2 (5)	1 (6)	3 (5)
Unmutated, n (%)	2 (6)	9 (12)	0 (0)	11 (9)	0 (0)	7 (18)	1 (6)	8 (13)
Unknown or missing, n (%)	29 (91)	62 (81)	12 (80)	103 (83)	6 (100)	32 (78)	15 (88)	53 (83)
Comorbidity index^a								
0, n (%)	22 (69)	46 (60)	11 (73)	79 (64)	2 (33)	24 (59)	10 (59)	36 (56)
1-2, n (%)	8 (25)	22 (29)	1 (7)	31 (25)	3 (50)	13 (32)	4 (24)	20 (31)
≥3, n (%)	2 (6)	9 (12)	3 (20)	14 (11)	1 (17)	4 (10)	3 (18)	8 (13)
Blood leukocyte count (10⁹/L)								
Mean (standard deviation)	90.4 (98.5)	108.0 (81.5)	158.1 (91.5)	109.7 (88.7)	50.2 (61.1)	56.0 (52.9)	66.6 (64.3)	58.3 (56.1)
>100, n (%)	7 (22)	39 (51)	12 (80)	58 (47)	1 (17)	8 (20)	4 (24)	13 (20)
Year of CLL diagnosis								
2005-2007, n (%)	26 (81)	19 (25)	2 (13)	47 (38)	5 (83)	21 (51)	4 (24)	30 (47)
2008-2010, n (%)	6 (19)	35 (45)	3 (20)	44 (35)	1 (17)	18 (44)	4 (24)	23 (36)
2011-2015, n (%)	0 (0)	23 (30)	10 (67)	33 (27)	0 (0)	2 (5)	9 (53)	11 (17)
Time to progression^c <2 y, n (%)	NA	NA	NA	NA	5 (83)	19 (46)	7 (41)	31 (48)
Treatment regimens								
FC/FCR, n (%)	18 (56)	45 (58)	8 (53)	71 (57)	0 (0)	10 (24)	2 (12)	12 (19)
B/BR, n (%)	2 (6)	19 (25)	7 (47)	28 (23)	1 (17)	14 (34)	8 (47)	23 (36)
Regimens other than FC/FCR or B/BR, n (%)	12 (38)	13 (17)	0 (0)	25 (20)	5 (83)	17 (41)	7 (41)	29 (45)
Chlorambucil without monoclonal antibody, n (%)	8 (25)	5 (6)	0 (0)	13 (10)	2 (33)	4 (10)	0 (0)	6 (9)

(Continues)

**TABLE 1** (Continued)

Patient characteristic	First-line treatment initiation period				Second-line treatment initiation period			
	Early: 2005-2008 (N = 32)	Middle: 2009-2013 (N = 77)	Late: 2014-2015 (N = 15)	In total: 2005-2015 (N = 124)	Early: 2006 ^b -2008 (N = 6)	Middle: 2009-2013 (N = 41)	Late: 2014-2015 (N = 17)	In total: 2006 ^b -2015 (N = 64)
Monoclonal antibody-based therapies ^d alone or in combination, n (%)	1 (3)	6 (8)	0 (0)	7 (6)	1 (17)	7 (17)	4 (24)	12 (19)
Other ^e , n (%)	3 (9)	2 (3)	0 (0)	5 (4)	2 (33)	6 (15)	3 (18)	11 (17)

Abbreviations: B, bendamustine; BR, bendamustine-rituximab; FC, fludarabine-cyclophosphamide; FCR, fludarabine-cyclophosphamide-rituximab; FISH, fluorescence in situ hybridization; IgHV, immunoglobulin heavy chain variable; NA, not applicable.

^aThe comorbidity index was derived according to the Charlson comorbidity index (17), as applicable with Finnish Hematology Registry data: a patient received 1 score from each of the following comorbidities: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular diseases, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes; 2 scores from renal disease; and 3 scores from liver disease and from any tumour.

^bThe first second-line treatments were initiated in 2006.

^cTime from the end of the first-line treatment to the start of the second-line treatment.

^dMonoclonal anti-CD20 antibody (rituximab, obinutuzumab) or monoclonal anti-CD52 antibody (alemtuzumab) alone or in combination, excluding FCR and BR (including rituximab). This group included in first-line 1 and in second-line 3 combination therapies with chlorambucil and rituximab.

^eTherapies with eg glucocorticoids, cyclophosphamide or fludarabine excluding therapies in any of the other categories (FC/FCR, B/BR, chlorambucil, or monoclonal antibody).

obtained from the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District (HUS/1272/2016). All patients included in the FHR had provided their informed consent prior to participating in studies utilising FHR data.

3 | RESULTS

3.1 | Patient characteristics in first-line

In total, 124 patients initiated first-line treatment during the study: 32 in the *early* (2005-2008), 77 in the *middle* (2009-2013) and 15 in the *late* (2014-2015) periods (Table 1). The median age was 66 years in the *early* and *middle* periods, and 69 years in the *late* period. The proportion of male patients was 75% (24/32), 70% (54/77) and 47% (7/15) in the *early*, *middle* and *late* periods, respectively. The use of FISH testing before first-line treatment increased over time: from 34% (11/32) in the *early* period to 87% (13/15) in the *late* period. The IgHV mutation status was tested for a minority (17% [21/124]) of patients with slight increase over time. In the *early*, *middle* and *late* periods, 6% (2/32), 12% (9/77) and 20% (3/15) of patients had a comorbidity index of 3 or more, respectively. The median follow-up times were 6.3, 4.1 and 1.3 years in the *early*, *middle* and *late* periods, respectively.

3.2 | Patient characteristics in second-line

During the study, 64 patients initiated second-line treatment: 6 in the *early*, 41 in the *middle* and 17 in the *late* period (Table 1). The median age was 71 years, with little variation between the time periods. The use of FISH testing before second-line treatment increased over time from 50% (3/6) of patients in the *early* period to 88% (15/17) in the *late* period. The IgHV mutation status was not tested in the *early* period, and was available for a minority of patients in the *middle* (22% [9/41]) and *late* periods (12% [2/17]). The comorbidity index

was 3 or more in 17% (1/6), 10% (4/41) and 18% (3/17) of patients in the *early*, *middle* and *late* periods, respectively.

3.3 | Treatment patterns in first-line

The most frequently used first-line treatments (>50% of patients) were FC/FCR irrespective of the treatment initiation period (Table 1). The use of B/BR increased over time from 6% (2/32) of patients in the *early* period to 25% (19/77) and 47% (7/15) in the *middle* and *late* periods. Treatment with regimens other than FC/FCR or B/BR declined from 38% (12/32) of patients in the *early* to 17% (13/77) in the *middle* and no patients in the *late* period. Within this group, chlorambucil without a monoclonal antibody was most common in the *early* period (25% [8/32] of patients), while monoclonal antibody-based therapies increased in the *middle* period (8% [6/77] of patients).

3.4 | Treatment patterns in second-line

Second-line treatment with FC/FCR varied from no patients in the *early* to 24% (10/41) in the *middle* and 12% (2/17) in the *late* period (Table 1). Treatment with B/BR increased over time, from 17% (1/6) of patients in the *early*, 34% (14/41) in the *middle* and 47% (8/17) in the *late* period. On the contrary, treatment with regimens other than FC/FCR or B/BR declined from 83% (5/6) in the *early* to 41% (17/41, 7/17) in both the *middle* and *late* periods. Among the other regimens, treatment with chlorambucil without monoclonal antibody declined from 33% (2/6) of patients in the *early* to 10% (4/41) of patients in the *middle* and no patients in the *late* period. In contrast, the use of monoclonal antibody-based therapies (excluding chlorambucil) appeared to increase over time, from 17% of patients in the *early* (1/6) and *middle* (7/41) periods to 24% (4/17) in the *late* period.

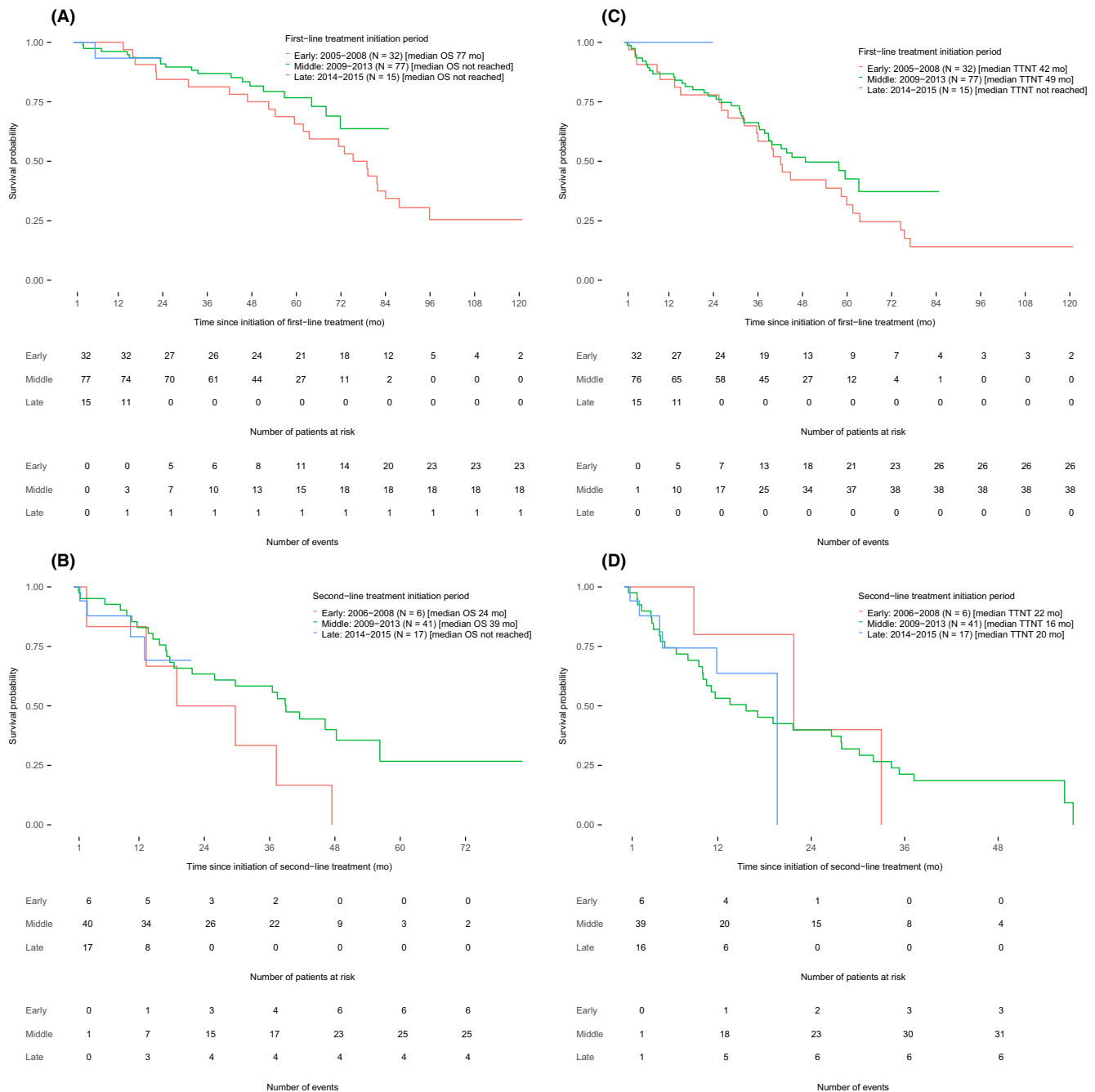


FIGURE 1 Kaplan-Meier survival curves for first-line overall survival (OS) (Panel A), second-line OS (Panel B) (OS), first-line time-to-next-treatment (TTNT) (Panel C), and second-line TTNT (Panel D), by treatment initiation period. Log-rank *P*-values for first-line OS (Panel A): *early vs. middle* 0.154, *early vs. late* 0.969, *middle vs. late* 0.917. Log-rank *P*-values for second-line OS (Panel B): *early vs. middle* 0.072, *early vs. late* 0.646, *middle vs. late* 0.832. Log-rank *P*-values for first-line TTNT (Panel C): *early vs. middle* 0.262, *early vs. late* 0.076, *middle vs. late* 0.097. Log-rank *P*-values for second-line TTNT (Panel D): *early vs. middle* 0.629, *early vs. late* 0.217, *middle vs. late* 0.608. OS, overall survival; TTNT, time-to-next-treatment

3.5 | Overall survival in first-line

The median OS after any first-line treatment initiation was 82 months (95% CI 73-not available). When the treatment was initiated in the *early* period, median OS was 77 months, while the median OS was not reached for the *late* and *middle* periods (Figure 1A). Based on the adjusted Cox regression model (Table 2), treatment initiation in the *middle* vs *early* period decreased the risk of death (adjusted HR 0.32, 95% CI

0.12-0.85). The decreased risk of death in the *late vs early* period did not reach statistical significance (adjusted HR 0.27, 95% CI 0.03-2.77).

3.6 | Overall survival in second-line

For all 64 patients who received second-line treatment, the median OS was 37 months (95% CI 26-48). The median OS appeared longer during the *middle* (39 months) compared to the *early* period



(24 months), without reaching statistical significance (Figure 1B). The median OS was not reached for the *late* period. A statistically non-significant decrease in the risk of death was observed in the *middle* or *late* vs the *early* period, based on the adjusted Cox regression models (adjusted HR for the *middle* period 0.31, 95% CI 0.06-1.71; adjusted HR for the *late* period 0.11, 95% CI 0.01-1.92) (Table 2).

3.7 | Associated factors

When factors associated with OS were investigated, the reduction in the risk of death was less pronounced in first-line B/BR treatment, compared with FC/FCR (FC/FCR vs. B/BR as reference: adjusted HR 0.29, 95% CI 0.10-0.85, *P*-value 0.048), or other regimens (regimens other than FC/FCR or B/BR vs. B/BR as reference: adjusted HR 0.22, 95% CI 0.07-0.67, *P*-value 0.009). The results for second-line treatment with B/BR suggested it could be associated with inferior OS, compared to other regimens, without reaching statistical significance (Table 3).

Other factors increasing the risk of death after first-line treatments included higher age, comorbidity index and leukocyte count (Table S1 in Appendix S2). These factors were not associated with second-line OS.

3.8 | Time-to-next-treatment

The median first-line TTNT for all patients was 45 months (95% CI 40-63), with a statistically non-significant improvement from the *early* to *middle* period (Figure 1C). After adjustment for other factors, TTNT was found to be longer for patients initiating first-line treatment in the *middle* vs *early* period (adjusted HR 0.36, 95% CI 0.15-0.87) (Table 2). The corresponding results for the *late* period were not available as no one proceeded to the next treatment during the follow-up.

The median second-line TTNT was 19 months, without signs of time trend between the periods (Figure 1D; all comparisons non-significant). When adjusting for other factors in the Cox regression model, no association was observed between time period of second-line treatment initiation and TTNT (Table 2).

The TTNT after first-line treatment initiation was shorter for patients with a higher comorbidity index and leukocyte count (Table S2 in Appendix S2). No factors were associated with TTNT after second-line treatment initiation. Treatment regimens were not associated with TTNT.

4 | DISCUSSION

This study showed for the first time in Finland that patients with CLL treated in the more recent time periods had a trend towards prolonged first- and second-line OS. The reduction in the risk of death was less pronounced when patients received first-line treatment with B/BR compared to FC/FCR or other regimens. A similar

trend was seen in patients treated with B/BR at second-line. First-line TTNT was longer for patients treated in the recent years, while second-line TTNT did not improve over time.

4.1 | Treatment patterns

We observed changes in first-line treatment practice over time, with increasing use of B/BR and decreasing use of chlorambucil-based therapies. FC/FCR were expectedly the most common first-line treatments throughout the study period, as FC was previously and FCR is today the recommended standard first-line treatment for fit patients with CLL, in the absence of del(17p).^{7,8} The increasing use of B/BR as first-line treatment over time was expected, as BR was licensed in Europe in 2010, and became recommended at first-line when FCR is contraindicated.¹⁰ Our result, showing that first-line treatment with B/BR increased and chlorambucil-based therapies declined still during 2014-2015 in Finland, complements the findings in Swedish and German clinical practices where a similar trend towards increasing use of B/BR was observed until the end of study follow-up in 2013.^{11,15,18} The overall changes we observed in first-line treatments over time, were in line with the Finnish treatment recommendations,¹⁰ and the reported treatment patterns in Sweden 2003-2013¹⁵ and Germany 2009-2013.¹¹

The observed change in second-line treatment after 2008, with FCR, BR and other monoclonal antibody-based therapies (mainly rituximab) becoming the mainstay, is in line with reported second-line treatment patterns in Sweden¹⁵ and international treatment guidelines.⁷⁻⁹ As the Finnish treatment guidelines do not provide an order for recommended second-line treatments, our study provides a valuable insight into routine clinical practice in Finland.

4.2 | Overall survival

The trend towards improved survival for patients who initiated first-line treatment during the later years corroborates the results from real-world studies in Denmark,¹⁴ Norway,² Germany and the United States.³ The fact that in our study, the improved survival in frontline setting in the later years reached statistical significance after adjusting the analysis for age, disease status, treatments and other factors, indicates that the trend towards improved survival over time was dependent on these multiple factors. At the same time, residual confounding likely remained even after the adjustment, possibly from improvements in supportive care,¹² or increasing use of novel therapies in the subsequent treatment lines.

This is the first study to report a trend towards prolonged survival of patients who initiated their second-line treatment in the later years compared to earlier. A prior Swedish study¹⁵ found no significant improvement in the second-line OS over time up to 2013, which may be explained by the high use of chlorambucil even in 2011-2013. Furthermore, our study included patients who initiated second-line treatment in 2014-2015 allowing to assess the shift in prescribing practices over time from exclusively chemotherapy to chemoimmunotherapy regimens. However, the trend toward prolonged survival in

TABLE 2 Unadjusted and adjusted^a hazard ratios (HRs) for overall survival (OS) and time-to-next-treatment (TTNT) from first- and second-line treatment initiation, by treatment initiation period

Treatment initiation period	Overall survival (OS)				Time-to-next-treatment (TTNT)			
	Unadjusted Cox model		Adjusted ^a Cox model		Unadjusted Cox model		Adjusted ^a Cox model	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
At first-line (N = 124)								
Early: 2005-2008 (N = 32)	1 (reference)	-	1 (reference)	-	1 (reference)	-	1 (reference)	-
Middle: 2009-2013 (N = 77)	0.62 (0.32-1.20)	0.146	0.32 (0.12-0.85)	0.043	0.75 (0.45-1.24)	0.248	0.36 (0.15-0.87)	0.039
Late: 2014-2015 (N = 15)	0.81 (0.10-6.68)	0.841	0.27 (0.03-2.77)	0.328	NA ^b	NA ^b	NA ^b	NA ^b
At second-line (N = 64)								
Early: 2006 ^c -2008 (N = 6)	1 (reference)	-	1 (reference)	-	1 (reference)	-	1 (reference)	-
Middle: 2009-2013 (N = 41)	0.45 (0.18-1.10)	0.016	0.31 (0.06-1.71)	0.260	1.34 (0.41-4.42)	0.464	1.54 (0.27-8.89)	0.591
Late: 2014-2015 (N = 17)	0.55 (0.15-2.00)	0.315	0.11 (0.01-1.92)	0.356	1.13 (0.28-4.57)	0.814	1.67 (0.17-16.75)	0.711

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable.

^aAdjusted for age, gender, Binet stage, cytogenetic lesions (fluorescence in situ hybridization), immunoglobulin heavy chain variable mutational status, comorbidity index, blood leukocyte count, year of chronic lymphocytic leukaemia diagnosis, time to progression (only second-line analyses), treatment regimen at first-line, and treatment regimen at second-line (only second-line analyses).

^bNo events during the late period (no one proceeded to next treatment).

^cThe first second-line treatments were initiated in 2006.

the recent years in second-line did not remain statistically significant after adjusting for other factors, probably due to the small sample size.

In summary, we detected a time trend towards longer survival among patients with CLL initiating first- and second-line treatments in recent years in Finland. The improvement was likely influenced by

multiple factors in patient characteristics and treatments, and presumably factors unexplored in this study. To further improve the prognosis of patients with CLL, further research is needed to explore the factors influencing their survival over time. Future studies on treatment effects since the arrival of BCR inhibitors would also be beneficial.

Treatment regimen	Overall survival (OS)	
	Adjusted ^a HR (95% CI)	P-value
At first-line (N = 124)^b		
FC/FCR: Fludarabine-cyclophosphamide or fludarabine-cyclophosphamide-rituximab (N = 71)	0.29 (0.10-0.85)	0.048
B/BR: Bendamustine or bendamustine-rituximab (N = 28)	1 (reference)	-
Regimens other than FC/FCR or B/BR (N = 25)	0.22 (0.07-0.67)	0.009
At second-line (N = 64)^b		
FC/FCR: Fludarabine-cyclophosphamide or fludarabine-cyclophosphamide-rituximab (N = 12)	0.36 (0.07-1.84)	0.141
B/BR: Bendamustine or bendamustine-rituximab (N = 23)	1 (reference)	-
Regimens other than FC/FCR or B/BR (N = 29)	0.33 (0.07-1.54)	0.228

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aAdjusted for treatment initiation period, age, gender, Binet stage, cytogenetic lesions (fluorescence in situ hybridization), immunoglobulin heavy chain variable mutational status, comorbidity index, blood leukocyte count, year of chronic lymphocytic leukaemia diagnosis, time to progression (only second-line analyses), treatment regimen at first-line, and treatment regimen at second-line (only second-line analyses).

^bAdjusted hazard ratios for all included factors are presented in Table S1 in Appendix S2.

TABLE 3 Association between first- and second-line treatment regimens and overall survival (OS)



4.3 | Treatment regimens and overall survival

To our knowledge, this is the first observational study in routine clinical setting to report that first-line treatment with B/BR may result in inferior OS, compared to other regimens. A similar, statistically non-significant, trend towards inferior OS was observed with B/BR in second-line. These results were, however, likely influenced by other treatments and patient characteristics unexplored in this study. Although B/BR is commonly recommended,^{8,19} the evidence from clinical trials on its superiority as first-line treatment is limited.²⁰ Its evidence as second-line treatment is even more sparse, as the pivotal clinical study was a small single-arm phase 2 trial²¹ and phase 3 studies have shown a poor effect of BR at relapse compared to novel agents.²²⁻²⁴ Although a recent observational study concluded that BR is an effective salvage at first relapse,²⁵ the results were based on an indirect comparison of OS in patients treated with ibrutinib not eligible for BR. As patients in the ibrutinib group were relapsed or refractory to FCR, BR, or any other alternative, their underlying health status was poor. Thus, the reported effect of BR may have resulted from this underlying difference between the compared groups. Considering the increasing use of BR and rather limited evidence from clinical trials²⁰⁻²³ and observational studies,²⁵ our results warrant further research on the use of B/BR in clinical practice.

4.4 | Time-to-next-treatment

We found a trend towards delayed first-line TTNT when patients initiated treatment in the recent years. As for OS, the fact that the longer TTNT reached statistical significance in the adjusted analysis suggests that the improvement is dependent on multiple factors.

In contrast to first-line, second-line TTNT did not improve over time, a finding observed in the Swedish population as well.¹⁵ This indicates that second-line treatments used in recent years may not prolong time to progression compared to the earlier treatments, thus warranting a need for optimising disease management in second-line.

4.5 | Other associated factors

Apart from treatment regimens, the other factors associated with first-line treatment outcomes in our study: higher comorbidity or lower performance status,^{18,26} higher leukocyte count,²⁷ and older age (associated with OS only),^{18,27-29} have also been identified previously as risk factors for shorter survival time and TTNT. Contrary to a prior study,³⁰ we did not identify short time to progression in the first-line as a risk factor for short survival in the second-line.

4.6 | Methodological considerations

This study is the first to report temporal trends in CLL treatment and outcomes after BR became a standard first-line option for elderly patients, and the first to investigate time trends using routine practices data with the possibility to adjust the analyses for differing clinical

characteristics and treatments. The FHR data source enabled a more comprehensive detection of patients diagnosed with CLL and a wider range of patient and treatment characteristics, compared to exclusive use of the national cancer register.^{2,12,14} This study was limited by a relatively small population and partially missing data for some key variables such as FISH and IgHV, limiting the full potential to control for confounding in the analyses. Moreover, data from one university hospital representing the metropolitan area were used, limiting the generalisability of the results to rural settings. In particular, elderly patients may have been under-represented in the study population as they are more likely to be treated outside of the university hospitals. This is also one reason for that the percentual proportion of FISH testing was lower than recommended in clinical practice in Finland, especially during the early years. As these biological data are in important role in ascertaining patient outcomes, improvements in diagnostic practices may have aided treatment selection in the recent, but not in the early years. Finally, especially in second-line treated patients, a relatively small sample size coupled with limited follow-up, precluded reaching median OS and TTNT and the detection of statistically significant effects.

5 | CONCLUSIONS

Changes in first-line treatment practice over time with increased use of B/BR and decreased use of chlorambucil-based therapies reflected Finnish guidelines. A similar trend was observed in second-line, providing valuable evidence on the change in treatment patterns in Finland after 2008. Our findings are similar to observations in Sweden and in line with international treatment guidelines. Patients treated in the recent years showed a trend towards extended first- and second-line survival. First-line treatment with B/BR resulted in inferior OS compared to other regimens, and a similar trend was detected for second-line treatment. Hence, further research on the use of B/BR in clinical practice is warranted, particularly in larger populations with opportunities to adjust for patient characteristics influencing treatment selection. Despite the fact that TTNT after first-line treatment initiation was longer for patients treated in the recent years, the lack of improvement in second-line indicates a need for optimising disease management after first-line. The improved outcomes over time were likely influenced by patient characteristics, treatments, and presumably other factors unexplored in this study. To improve the prognosis of patients with CLL, further research is needed to explore the factors influencing their survival over time. This was a Finnish study and owing to similarities in population characteristics and health-care policies, the results are comparable to other Nordic countries.

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CONFLICT OF INTEREST

VL reports no conflict of interest. KMH, JM and RK are employed by StatFinn & EPID Research, which is a contract research organization that performs commissioned pharmacoepidemiological studies and thus its employees have been and currently are working in collaboration with several pharmaceutical companies. AL and TMJ are employees of Janssen-Cilag.

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