

IGHV mutational status and outcome for patients with chronic lymphocytic leukemia upon treatment: a Danish nationwide population-based study

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ABSTRACT

Patients with chronic lymphocytic leukemia and unmutated immunoglobulin heavy-chain variable region gene (IGHV) have inferior survival from time of treatment in clinical studies. We assessed real-world outcomes based on mutational status and treatment regimen in a nationwide population-based cohort, comprising all 4,135 patients from the Danish chronic lymphocytic leukemia registry diagnosed between 2008 and 2017. In total, 850 patients with known mutational status received treatment: 42% of patients received intensive chemoimmunotherapy consisting of fludarabine, cyclophosphamide plus rituximab, or bendamustine plus rituximab; 27% received chlorambucil in combination with anti-CD20 antibodies or as monotherapy, and 31% received other, less common treatments. No difference in overall survival from time of first treatment according to mutational status was observed, while treatment-free survival from start of first treatment was inferior for patients with unmutated IGHV. The median treatment-free survival was 2.5 years for patients treated with chlorambucil plus anti-CD20, and 1 year for those who received chlorambucil monotherapy. The 3-year treatment-free survival rates for patients treated with fludarabine, cyclophosphamide plus rituximab, and bendamustine plus rituximab were 90% and 91% for those with mutated IGHV, and 76% and 53% for those with unmutated IGHV, respectively, and the 3-year overall survival rates were similar for the two regimens (86–88%). Thus, it appears that, in the real-world setting, patients progressing after intensive chemoimmunotherapy as first-line therapy can be rescued by subsequent treatment, without jeopardizing their long overall survival. Intensive chemoimmunotherapy remains a legitimate option alongside targeted agents, and part of a personalized treatment landscape in chronic lymphocytic leukemia, while improved supportive care and treatment options are warranted for unfit patients.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in the Western world and half of the patients with this condition require treatment within 5 years of diagnosis.¹ According to Danish national CLL guidelines,^{2,3} standard first-line treatment includes fludarabine, cyclophosphamide plus rituximab (FCR) for younger, fit patients,^{4,5} and bendamustine plus rituximab (BR) for patients above 65 years old.^{6,7} Furthermore, chlorambucil, either as monotherapy or com-



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bined with anti-CD20 antibodies (CD20-chlorambucil), is recommended for unfit patients with significant comorbidity.⁸ Patients with del(17p)/*TP53* mutations are treated with targeted agents (ibrutinib, idelalisib-rituximab or venetoclax).^{9,10} The Danish guidelines are updated biannually and the changes over time have been described previously.³

Immunoglobulin heavy-chain variable region gene (IGHV) mutational status is an acknowledged prognostic factor in CLL and is included in the disease-specific International Prognostic Index (CLL-IPI).^{11,12} In previous studies, patients with unmutated IGHV (U-CLL) had shorter survival from diagnosis compared with patients with mutated IGHV (M-CLL), and inferior remission duration and survival from the start of chemoimmunotherapy.^{5,6,12-18}

We present data on the impact of IGHV mutational status on overall survival (OS) and treatment-free survival (TFS) from the time of treatment in the world's largest, nationwide, population-based cohort of consecutive, unselected patients with CLL receiving different treatment regimens.

Methods

Data sources and study population

The Danish CLL registry contains data on all patients diagnosed with CLL in Denmark since 2008.¹⁹ As of August 2017, the registry contained information on 4,135 CLL patients, who were included in the present study (Figure 1A). The CLL registry contains data on sex, dates of birth, diagnosis, and treatment, type of treatment, IGHV mutational status, and other disease characteristics including cytogenetics, *TP53* mutations, and β_2 -microglobulin levels at the time of diagnosis. Information on vital status is included in the CLL registry through regular linkage with the Danish Civil Registration System.^{20,21} Patients with missing data regarding key variables were excluded from the study. Patients were followed from the date of diagnosis in 2008-2017, until the time of death, emigration, or August 2017, whichever came first. All treatments of minimum one series were considered. For the subset of patients who had received first-line treatment at Odense University Hospital, in the Capital Region, or in the Zealand Region between 2008-2016, detailed information on second-line treatment was collected through review of the patients' clinical records. Together, these regions cover over half of the Danish population. These patients were followed from the date of diagnosis in 2008-2016, until the time of death, emigration, or mid-2018 (ranging from May-November, depending on the date of the patients' record review), whichever came first.

Statistical analysis

The patients' characteristics are reported for those with U-CLL and M-CLL and for treatment groups, and compared using parametric or non-parametric descriptive statistics, depending on the data distribution. Kaplan-Meier survival analyses were used to assess survival. TFS from the time of diagnosis (TFS_d) was defined as the time to first treatment, end of follow-up, or death, whichever came first. OS was determined starting from either the time of diagnosis (OS_d) or the time of first-line treatment initiation (OS_i), until death, or end of follow-up, whichever came first. TFS_i, defined as the time from initiation of first-line treatment to initiation of second-line treatment, death or end of follow-up, whichever came first, was studied for the sub-popu-

lation with detailed information on second-line treatment from medical record review. OS, and TFS, were the primary endpoints of the study, while OS_d and TFS_d were secondary endpoints. We explored the prognostic significance of IGHV status, treatment regimen, del(17p) status, elevated β_2 -microglobulin level, sex, age, and Binet stage for risk of death or treatment, using multi-variable Cox regression models to calculate hazard ratios (HR). All HR presented have been adjusted for these variables, except for TFS_i, which was adjusted for sex, age, del(17p)/*TP53*-mutation, and Binet stage. Unadjusted HR were calculated but are not presented in this paper as they were not of clinical relevance. Log-rank tests were used to test for homogeneity of outcomes between exposures. Data analysis was performed using STATA (StataCorp. 2015. Stata Statistical Software: Release 15.1 College Station: StataCorp LP, TX, USA)

Ethics

The study was approved by the Danish Health and Medicine Authorities (jr. n. 3-3013-1141/1) and the Danish Data Protection Agency (jr. n. RH-2015-96 03856). Results for subgroups including fewer than five patients were reported as "less than five" to ensure anonymity of individual patients, in accordance with Danish legislation.

Results

Characteristics at time of diagnosis of chronic lymphocytic leukemia

In total, 4,135 patients with a median follow-up time of 3.5 years were available for analysis, of whom two were excluded because of incomplete data. Information on IGHV mutational status was available for 3,197 (77%) patients, of whom 1,017 (32%) had U-CLL and 2,180 (68%) had M-CLL (Figure 1A). The characteristics of the patients, divided according to mutational status, are listed in Table 1. Among patients with unknown IGHV status, 255 (27%) received treatment during follow-up, compared with 481 (47%) of U-CLL and 369 (17%) of M-CLL patients. Distributions of sex and age at diagnosis were comparable between U-CLL and M-CLL patients, whereas prognostic factors were unevenly distributed, with del(13q) found in 28% of U-CLL patients and 53% of M-CLL patients. The prevalences of del(17p) (7%), del(11q) (16%) and trisomy(12) (16%) were higher among U-CLL patients than among M-CLL patients (4%, 2% and 11%, respectively). Of the U-CLL patients, 30% were categorized as having Binet stage B/C, compared with 13% of M-CLL patients, and 19% had a high level of β_2 -microglobulin (>4.0 mg/L), compared with 10% of M-CLL patients.

IGHV status and prognosis from the time of diagnosis

Patients with unmutated IGHV had shorter OS_d [HR=1.23, 95% confidence interval (95% CI): 1.01-1.50], compared with patients with M-CLL, and shorter TFS_d (HR=2.24, 95% CI: 1.95-2.57) (Figure 2A, B). The 5-year OS_d was 71% (95% CI: 68-74) for U-CLL patients and 81% (95% CI: 79-83) for those with M-CLL. The 5-year TFS_d for U-CLL patients was 31% (95% CI: 27-35), compared with 68% (95% CI: 65-70) for those with M-CLL. Patients with unknown IGHV status had a shorter 5-year OS_d (61%, 95% CI: 57-64) than patients with U-CLL or M-CLL, while the 5-year TFS_d (45%, 95% CI: 41-49) in this group was between that of U-CLL and M-CLL patients (*data not shown*). Overall, 92 (9%) patients with U-

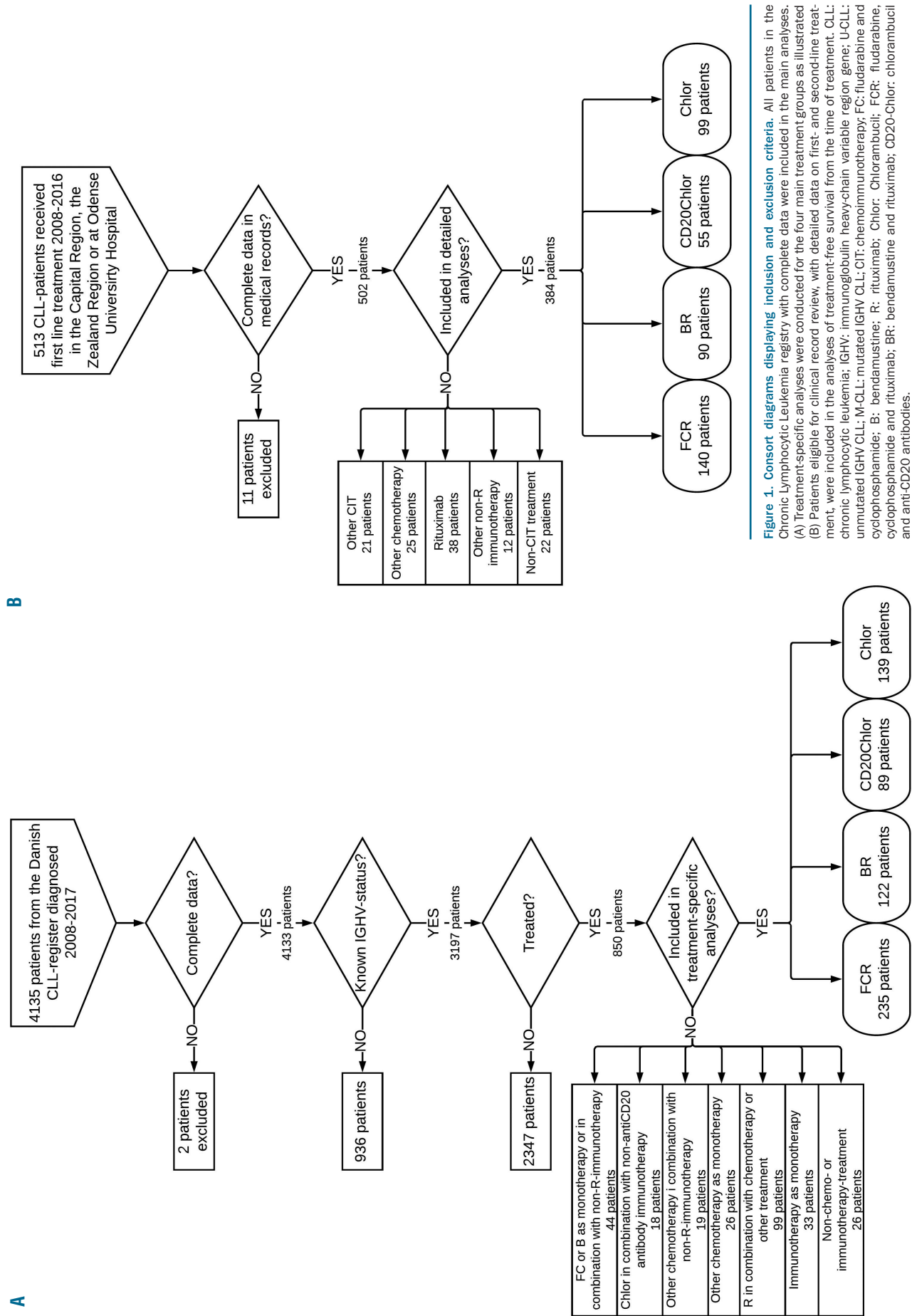


Figure 1. Consort diagrams displaying inclusion and exclusion criteria. All patients in the Chronic Lymphocytic Leukemia registry with complete data were included in the main analyses. (A) Treatment-specific analyses were conducted for the four main treatment groups as illustrated (B) Patients eligible for clinical record review, with detailed data on first- and second-line treatment, were included in the analyses of treatment-free survival from the time of treatment. CLL: chronic lymphocytic leukemia; IGHV: immunoglobulin heavy-chain variable region gene; U-CLL: unmutated IGHV CLL; M-CLL: mutated IGHV CLL; CIT: chemoimmunotherapy; FC: fludarabine and cyclophosphamide; B: bendamustine; R: rituximab; Chlor: Chlorambucil; FCR: fludarabine, cyclophosphamide and rituximab; BR: bendamustine and rituximab; CD20-Chlor: chlorambucil and anti-CD20 antibodies.

CLL, 263 (12%) patients with M-CLL, and 227 (24%) patients with unknown IGHV status died without receiving CLL treatment, while the numbers of events for OS_d and TFS_d were, respectively, 263 and 573 for patients with U-CLL, 384 and 632 for patients with M-CLL, and 360 and 482 for patients with unknown IGHV status.

Characteristics of treatment groups

Among the 850 treated patients with known IGHV status, 235 (28%) received FCR, 122 (14%) BR, 89 (10%) CD20-chlorambucil, 139 (16%), chlorambucil alone and 265 (31%) other, less common, treatments. Outcome was assessed separately for subgroups of patients treated with one of the four main treatment regimens (FCR, BR, CD20-chlorambucil and chlorambucil), as illustrated in Figure 1A. Patients who received other types of treatment were not studied in detail because of their small numbers. A subgroup of 99 patients received rituximab in combination with either an undefined type of chemotherapy, or other treatment: these patients were not, therefore, included in the detailed analyses. Baseline characteristics for treatment subgroups are detailed in Table 2. The median time of follow-up from treatment was 3.9 years for patients given FCR, 2.8 years for those given chlorambucil, and 2.1 years for patients treated with BR or CD20-chlorambucil. Patients treated with FCR were younger at the time of treatment (median 62 years) than patients treated with BR (median 70 years), while patients treated with CD20-chlorambucil (median 78 years) or chlorambucil (median 80 years) were the oldest. Binet B/C and U-CLL were more common among FCR-treated patients (56% and 64%, respectively) than among patients treated with BR, CD20-chlorambucil, or chlorambucil (34-42% and 52-58%, respectively). A smaller proportion of FCR-treated patients had a high β₂-microglobulin level or high/very high CLL-IPi score, compared with the other treatment groups (Table 2).

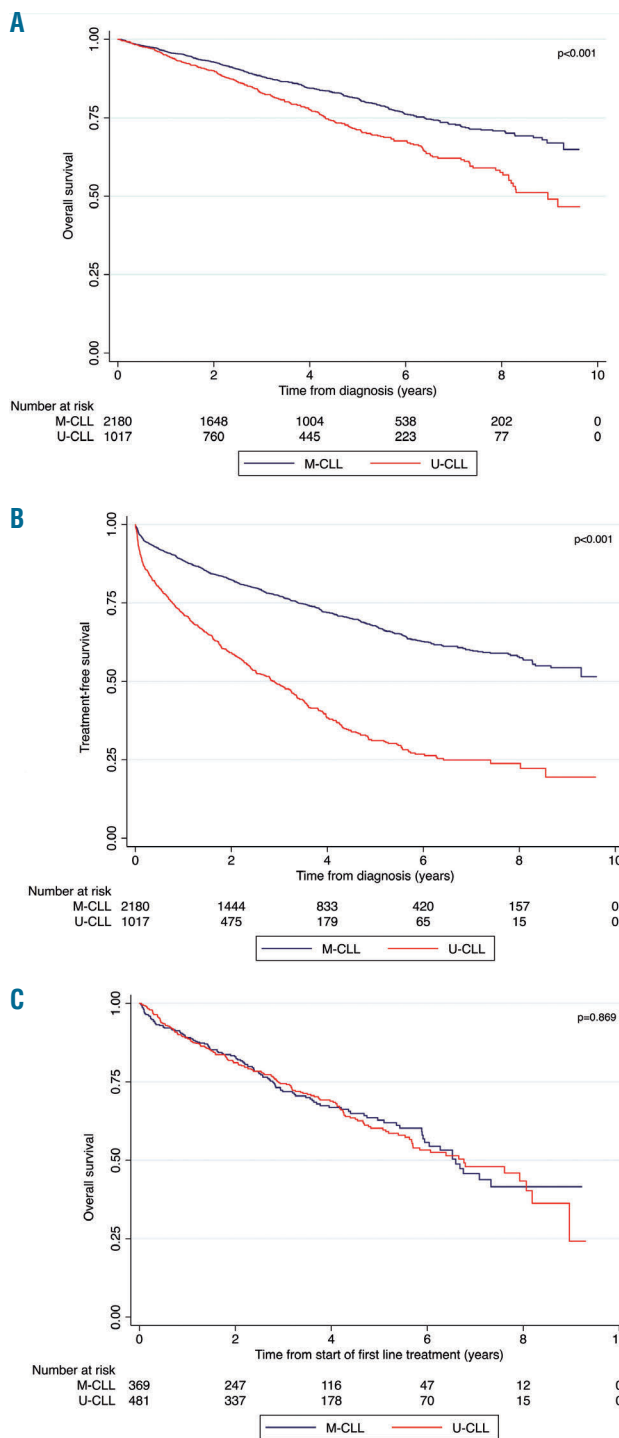
Table 1. Baseline characteristics and demographics at time of diagnosis for patients with chronic lymphocytic leukemia with unmutated, mutated and unknown IGHV mutational status from the Danish CLL registry.

Mutational status	U-CLL	M-CLL	Unknown IGHV
Number of patients	1017	2180	936
Treated	481 (47%)	369 (17%)	255 (27%)
Median age (IQR), years	69 (62-76)	70 (63-77)	74 (66-82)
Male	651 (64%)	1292 (59%)	560 (60%)
Cytogenetic abnormalities			
Del(17p)	70 (7%)	91 (4%)	44(8%)
Del(11q)	152 (16%)	50 (2%)	47 (9%)
Trisomy 12	157 (16%)	219 (11%)	60 (11%)
Normal FISH	313 (33%)	613 (30%)	147 (28%)
Del(13q)	269 (28%)	1088 (53%)	236 (44%)
B2M >4.0 mg/L	151 (19%)	174 (10%)	116 (19%)
Binet stage B/C	308 (30%)	292 (13%)	216 (23%)
Number of events OS _d	263	384	360
Number of events TFS _d	573	632	482
Number of events OS _t	171	121	133

The figures are numbers and percentages within each column unless stated otherwise. *Patients with missing data excluded. CLL: chronic lymphocytic leukemia; IGHV: immunoglobulin heavy-chain variable region gene; U-CLL: unmutated IGHV CLL; M-CLL: mutated IGHV CLL; IQR: interquartile range; FISH; fluorescence *in situ* hybridization; B2M: beta-2-microglobulin; OS_d: overall survival from time of diagnosis; TFS_d: treatment-free survival from time of diagnosis; OS_t: overall survival from time of first-line treatment.

Overall survival after first-line treatment

The median follow-up time from first-line treatment was 2.9 years. No difference in OS_t was observed between patients with U-CLL (171 deaths) and those with M-CLL



(121 deaths) [3-year OS, 74% (95% CI: 70-78) and 72% (95% CI: 66-77), respectively] (Figure 2C). Patients with unknown IGHV status had an inferior OS_t compared with U-CLL and M-CLL patients (133 deaths) [3-year OS, 59% (95% CI: 53- 65)] (*data not shown*). No impact on OS_t was observed based on unmutated IGHV status (HR=0.99, 95% CI: 0.75-1.32), Binet stage B/C at diagnosis (HR 1.01, 95% CI: 0.76-1.35), or male sex (HR=0.97, 95% CI: 0.73-1.29). Age above 65 years at the time of treatment (HR=3.18, 95% CI: 2.12- 4.77), high β₂-microglobulin level (HR=1.92, 95% CI: 1.42-2.60), and del(17p) (HR=1.79,

95% CI: 1.21-2.65) were statistically significantly associated with shorter OS_t.

During follow-up, 40 patients treated with FCR, 11 with BR, 37 with CD20-chlorambucil and 94 with chlorambucil, died. No difference was observed in 3-year OS_t rates between patients treated with FCR (88%, 95% CI: 83-92%) and BR (86%, 95% CI: 75-93%) (Figure 3A), or between those treated with CD20-chlorambucil (59%, 95% CI: 47-70%) and chlorambucil monotherapy (53%, 95% CI: 45-61%) (Figure 3B). No statistically significant variation by IGHV-status was found for OS_t, regardless of

Table 2. Baseline characteristics of chronic lymphocytic leukemia patients from the Danish CLL registry divided by treatment group.

Treatment regimen	FCR	BR	CD20-C1b	C1b	Other
Number of patients	235	122	89	139	265
Median FU time, years ^a	3.9	2.1	2.1	2.8	3.1
Median age (IQR) ^a	62 (55–67)	70 (66–75)	78 (74–82)	80 (74–84)	71 (65–78)
Male	155 (66%)	87 (71%)	60 (67%)	80 (58%)	162 (61%)
U-CLL	150 (64%)	64 (52%)	47 (53%)	80 (58%)	140 (53%)
Del(17p) ^b	10 (4%)	6 (6%)	<5 (-)	9 (4%)	40 (16%)
B2M >4.0 mg/L ^b	25 (15%)	22 (24%)	20 (31%)	30 (31%)	37 (18%)
Clinical stage					
A	103 (44%)	81 (66%)	54 (61%)	90 (65%)	154 (58%)
B/C	132 (56%)	41 (34%)	35 (39%)	49 (35%)	111 (42%)
CLL-IPI ^b					
High/very high	35 (21%)	25 (28%)	22 (34%)	32 (34%)	71 (36%)
Intermediate	82 (50%)	34 (38%)	28 (44%)	42 (44%)	80 (41%)
Low	48 (29%)	31 (34%)	14 (22%)	21 (22%)	45 (23%)
Number of events OS _t , U-CLL	26	6	18	58	63
Number of events OS _t , M-CLL	14	5	19	36	47

Data are from time of diagnosis, and figures are numbers and percentages within each column unless otherwise stated.

^aFrom time of treatment. ^bPatients with missing data excluded. FCR, fludarabine, cyclophosphamide and rituximab; BR: bendamustine and rituximab; CD20-C1b: chlorambucil and anti-CD20 antibodies; C1b: chlorambucil; FU: follow-up; IQR: interquartile range; U-CLL: chronic lymphocytic leukemia with unmutated immunoglobulin heavy-chain variable region gene; B2M: beta-2-microglobulin; CLL-IPI: chronic lymphocytic leukemia international prognostic index; OS_t: overall survival from time of first-line treatment; M-CLL: chronic lymphocytic leukemia with mutated immunoglobulin heavy-chain variable region gene.

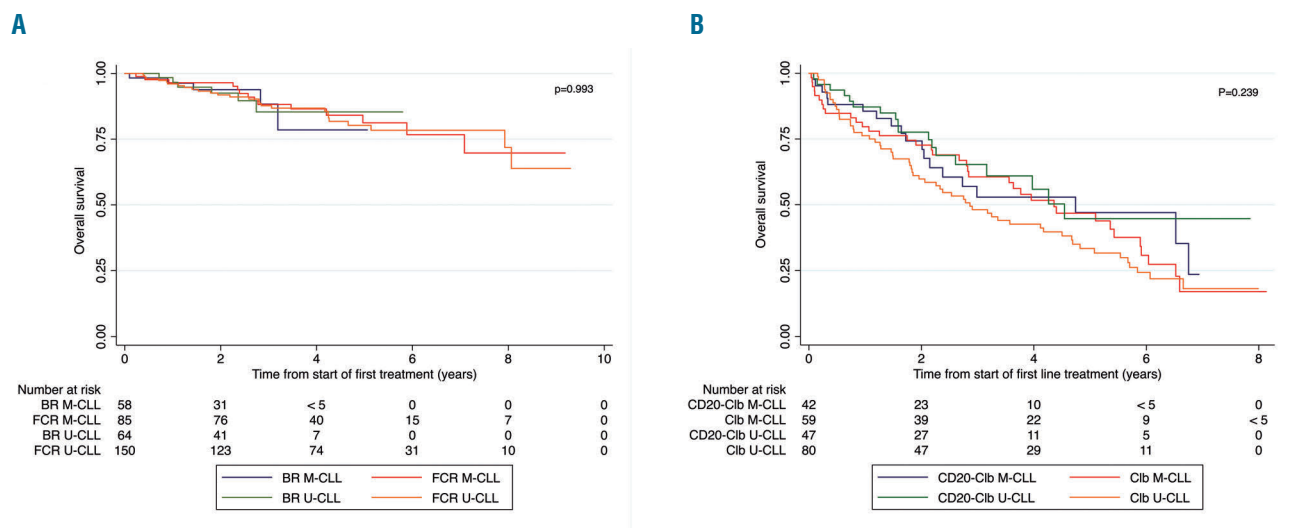


Figure 3. Overall survival of patients in the Danish CLL registry from the start of first-line treatment according to treatment group and immunoglobulin heavy-chain variable region gene mutational status. (A) Overall survival of patients treated with fludarabine, cyclophosphamide and rituximab (FCR), or bendamustine and rituximab (BR). (B) Overall survival of patients treated with chlorambucil and anti-CD20 antibodies (CD20-C1b) or chlorambucil monotherapy (C1b). M-CLL: chronic lymphocytic leukemia with mutated immunoglobulin heavy-chain variable region gene; U-CLL: chronic lymphocytic leukemia with unmutated immunoglobulin heavy-chain variable region gene.

whether the treatment regimens were pooled or separate [pooled: HR=1.15 (95% CI: 0.80-1.66), FCR-treated: HR=1.21 (95% CI: 0.53-2.77), BR-treated: HR=0.78 (95% CI: 0.14-4.15), CD20-chlorambucil-treated: HR=0.86 (95% CI: 0.38-1.91) and chlorambucil-treated: HR=1.31 (95% CI: 0.75-2.28)].

Treatment-free survival after first-line treatment

Among 513 patients eligible for record review, 11 were excluded because of incomplete data. Of the remaining 502 patients, 384 patients received one of the four major treatment regimens, which were studied in detail (Figure 1B). Comparing the four main treatment regimens, also including patients with unknown IGHV status, FCR produced the longest median TFS_t (6.0 years, 95% CI: 4.5-6.7 years), followed by BR (3.9 years, 95% CI: 3.4-5.1 years) (Figure 4A). The median TFS_t for chlorambucil-treated patients was 1 year (95% CI: 0.8-1.3 years), and that for CD20-chlorambucil-treated patients was 2.5 years (95% CI: 1.8-3.3) (Figure 4A). There were 39, 27, 11, and 36 events among U-CLL patients and 9, 7, 11, and 26 events among M-CLL patients, treated with FCR, BR, CD20-

chlorambucil, and chlorambucil, respectively. TFS_t was significantly shorter for patients with U-CLL than for those with M-CLL, following both intensive (FCR or BR) (HR=3.46, 95% CI: 1.93-6.19) and non-intensive (CD20-chlorambucil or chlorambucil) (HR=2.04, 95% CI: 1.24-3.37) treatment (Figure 4B). The 3-year TFS_t for U-CLL patients treated with intensive regimens (68%, 95% CI: 58-76) was inferior compared with that of M-CLL patients (91%, 95% CI: 81-96), also when treatments were assessed separately (FCR: HR=2.56, 95% CI: 1.19-5.50; BR: HR=7.50, 95% CI: 2.80-20.1) (Figure 4C). This was most evident for patients treated with BR, who had an estimated 3-year TFS_t of 91% (95% CI: 74-97%) for those with M-CLL and 53% (95% CI: 36-68%) for those with U-CLL, while the difference for FCR-treated patients was smaller (90%, 95% CI: 76-96%) and 76% (95% CI: 64-84%), respectively (Figure 4C). For CD20-chlorambucil- and chlorambucil-treated patients, no statistically significant difference according to IGHV status was observed when treatments were assessed separately (HR=2.19, 95% CI: 0.77-6.28 and HR=1.74, 95% CI: 0.97-3.12, respectively) (Figure 4D). Out of the 502 patients studied,

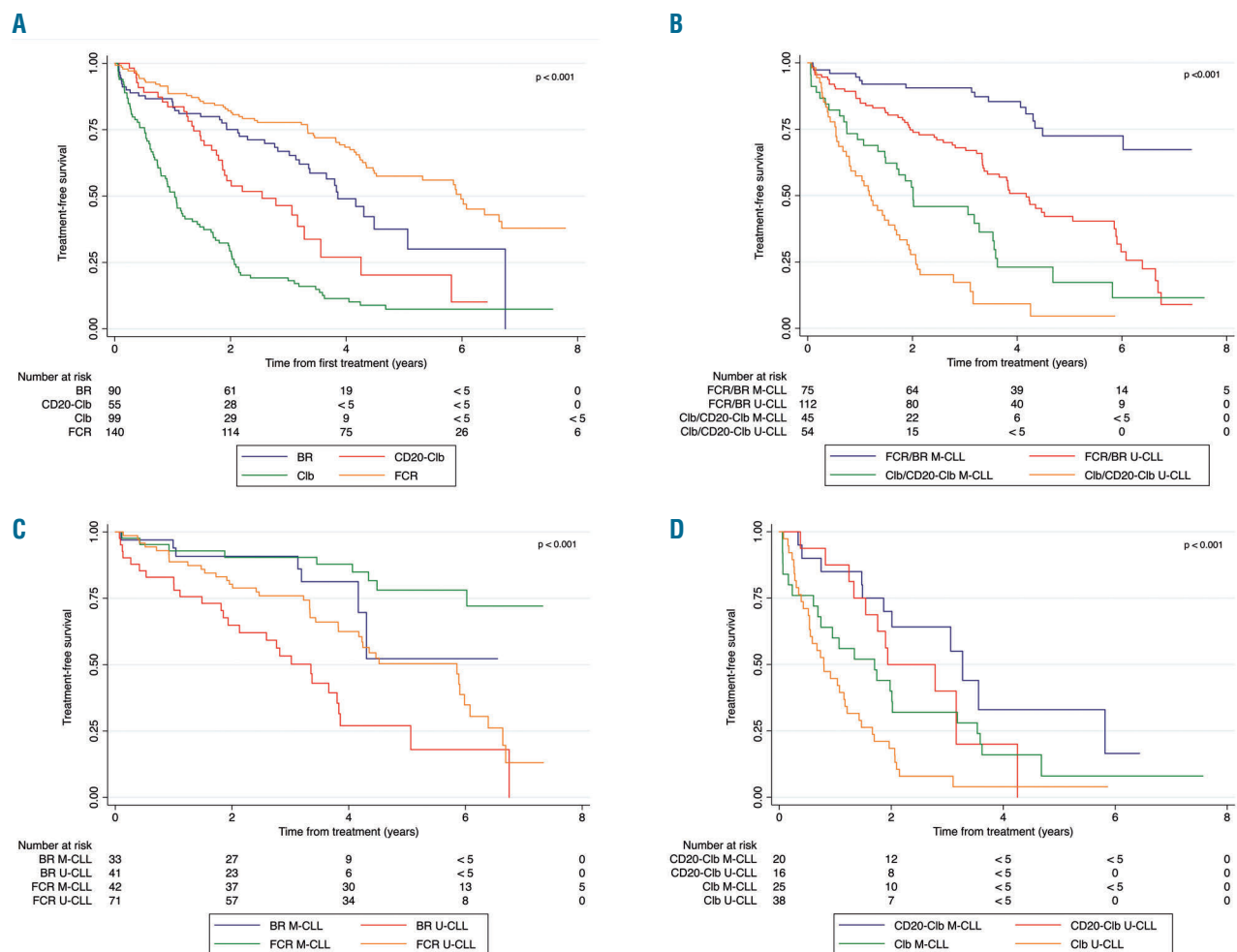


Figure 4. Treatment-free survival from the start of first-line treatment according to treatment group and immunoglobulin heavy-chain variable region gene mutational status. (A) Patients treated with fludarabine, cyclophosphamide and rituximab (FCR), bendamustine and rituximab (BR), chlorambucil (Cib), or chlorambucil and anti-CD20 antibodies (CD20-Cib), including patients with both known and unknown immunoglobulin heavy-chain variable region gene (IGHV) mutational status. (B) Patients fit for intensive treatment with FCR of BR, or unfit patients treated with Cib or CD20-Cib, and with IGHV mutated (M-CLL) or unmutated (U-CLL) CLL. (C) Patients treated with FCR or BR with U-CLL or M-CLL. (D) Patients treated with CD20-Cib or Cib with U-CLL or M-CLL.

233 received second-line treatment during follow-up. Among patients who received second-line treatment, the mutational status was known for 167 (72%), of whom 117 (70%) had U-CLL. Of these unmutated cases, 33 (28%) received targeted treatment, compared with six (12%) of mutated patients.

Discussion

We present real-world data on the prognosis of CLL, from diagnosis and from time of first-line treatment, based on IGHV mutational status from the hitherto largest nationwide, population-based cohort. The main novel finding is the lengthy OS_i of both M-CLL and U-CLL patients treated with either FCR or BR, despite inferior TFS_i of U-CLL patients; reflecting U-CLL patients' response to salvage treatment. We confirm previous findings of U-CLL being associated with shorter OS_d and TFS_d compared with M-CLL.¹²⁻¹⁴

In clinical trial reporting, progression-free survival (PFS), defined as the time until death or disease progression, is commonly used to evaluate treatment outcome. Previous studies have reported superior PFS for M-CLL patients compared with U-CLL,^{5,6,16,17} and M-CLL patients without del(17p) or del(11q) in particular have long PFS upon chemoimmunotherapy.¹⁷ The 3-year PFS rates reported in previous clinical trials with FCR (66-83%)^{5,6,16,22-24} or BR (77% for M-CLL)^{6,25} and in the real-world setting with FCR (60-80%),^{17,26} are high, but inferior to those achieved with ibrutinib-based treatment (83-96%).^{22,25,27,28} Upon chlorambucil treatment the median PFS was 9 months in a Swedish real-world setting²⁶ and 11 months in clinical trials,^{29,30} compared with 1.3-2.4 years upon CD20-chlorambucil treatment in clinical trials.²⁹⁻³²

Here we report the data for treatment-free survival, which can be clinically more relevant as many patients do not meet the International Workshop on CLL criteria for treatment at disease progression.³³ Our results reveal a superior TFS_i for M-CLL patients compared with U-CLL patients, when treated with FCR, BR, or non-intensive treatment regimens. We observed high 3-year TFS_i rates for M-CLL patients treated with FCR (90%) or BR (91%) and for U-CLL patients treated with FCR (76%), similar to the findings of a smaller retrospective study of BR-treated patients who had a 3-year TFS_i of 90%.³⁴ This is especially impressive considering the median age of 70 years of the patients treated with BR in our study. Only 6% of M-CLL patients in our study had high-risk cytogenetics, consistent with the long TFS_i of M-CLL patients that we observed.

A 3-year OS_i of 86-88% was demonstrated for patients treated with either FCR or BR. These findings are comparable with those from randomized clinical trials of FCR (84-91%)^{5,6,16,22-24} and BR (89-92%),^{6,25,35} and other real-world studies of FCR-treated patients (83-95%).^{17,26} However, the overall superior OS_i for M-CLL patients previously reported as a dichotomous variable^{4-6,16,17} and as a continuous variable,³⁶ was not observed in our study. This could reflect that the follow-up time in our study may have been too short for differences in OS_i to manifest, and that factors such as comorbidity and subsequent lines of treatment may have been unevenly distributed across groups. Furthermore, a tendency to favor FCR over other treatment options for patients with U-CLL was

observed. This might reflect physicians' choice of treatment intensification based on recognition of the inferior prognosis for this group of patients. More than twice as many U-CLL patients received second-line treatment and more than five times as many were given targeted agents compared with M-CLL patients. This is likely due to the shorter TFS_i of U-CLL patients, again in recognition of their inferior prognosis, and may in part explain why no difference in OS_i was observed.

A previous study demonstrated that the prognostic impact of IGHV status upon chemoimmunotherapy is not driven by a difference in complete remission rate, but rather by earlier relapse due to the aggressiveness of the disease in U-CLL patients.¹⁸ The long OS_i after treatment with FCR or BR for both U-CLL and M-CLL patients in our study emphasizes that patients who progress after first-line chemoimmunotherapy may be salvaged with targeted treatment, or even repeated chemoimmunotherapy. A recent conference presentation described superior PFS, improved OS, and less toxicity with ibrutinib plus rituximab compared with FCR; however, subgroup analyses indicated that the benefit was mainly for U-CLL patients.²² The findings were similar, also mainly with impact on U-CLL patients, for ibrutinib-based regimens in comparison with BR, although without a difference in OS.²⁵ Cross-over was not allowed in these studies; thus, it remains to be systematically assessed in a clinical trial whether patients with progressive disease may be salvaged with targeted agents in second-line treatment. In view of the long period off treatment in general, and the possibility of a clinical cure for a substantial subgroup of M-CLL patients, chemoimmunotherapy remains a legitimate treatment option with robust data on safety and long-term outcome in the era of targeted agents. Thus, we suggest that intensive chemoimmunotherapy should be part of a personalized treatment landscape in CLL alongside targeted treatment, with treatment options adapted based on shared decision-making, guided by robust data from clinical trials and real-world evidence.

We found that patients treated with chlorambucil as monotherapy had a poor TFS_i regardless of IGHV status. Within 1 year of initiation of first-line treatment with chlorambucil, 50% of the patients had had an event. Patients treated with CD20-chlorambucil, with a median age of 78 years and representing a frail patient population, had a median TFS_i of 2.5 years. A similar median TFS_i of 3.4 years was observed in patients of comparable age receiving CD20-chlorambucil in randomized controlled trials.³⁷ The superior outcome of patients treated with CD20-chlorambucil, compared with chlorambucil suggests that chlorambucil as monotherapy must be considered obsolete. As baseline characteristics were similar between the groups in our study, our findings indicate that chlorambucil should be replaced by CD20-chlorambucil or by more effective and less toxic novel treatments. Considering the results of our study, as well as those of clinical trials, new treatment options and improved supportive care are warranted for patients unfit for intensive chemoimmunotherapy. The recently published studies on venetoclax plus obinutuzumab and ibrutinib-based frontline therapy, compared with CD20-chlorambucil, broaden the options for these patients. Subgroup findings indicate that mainly U-CLL patients benefit from targeted therapy, as also seen when compared with intensive chemoimmunotherapy regimens.^{25,32,38,39}

In contrast to a clinical trial setting, inclusion of patients above 65 years and more patients with significant comorbidities in our cohort^{40,41} may have reduced the impact of IGHV status as a prognostic factor.⁴²⁻⁴⁴ Clinical trial populations in CLL studies exploring IGHV status and chemoimmunotherapy had a median age of 57-73 years,^{5,6,16,32} compared with 62-80 years in our study, further emphasizing the importance of assessing real-world data. The higher prevalence of elevated β_2 -microglobulin levels in the treatment groups with a higher median age in our study may reflect decreased renal function^{45,46} and thus the comorbidity of these patients, rather than more aggressive CLL. The impact of comorbidity and frailty in the real-world population reported here is also reflected by a 3-year OS_i of 59% for patients treated with CD20-chlorambucil compared with over 80% in the CLL11 trial.⁸

Cancer patients for whom data registration is incomplete have previously been found to have poorer outcome,⁴⁷ which was also seen for patients with unknown IGHV status in the present study, when comparing both OS_d and OS_i in these patients with those of patients with mutated or unmutated IGHV. Patients with unknown IGHV status had a superior TFS_d compared with that of U-CLL patients. This reflects that many patients with unknown IGHV status die, probably due to CLL-unrelated causes, without ever receiving treatment for CLL.

The main strength of this study is its nationwide cohort, without the selection bias introduced in clinical trials, and the near completeness of data. Inherent in the retrospective design of the study, patients were assigned therapy by the treating physicians based on clinical assessment of fitness and clinical guidelines, in line with the described age distribution. The discrepancy in baseline characteristics between the treatment groups is a weakness of our study, although we have adjusted for known dissimilarities between the groups. However, as stated above, factors such as number and type of subsequent lines of treat-

ments, and distribution of comorbidities across groups of patients, are unknown. Uneven distribution of these factors could in part explain the discrepancy between our results and those of previous studies regarding the significance of IGHV status in relation to OS_i. More patients were diagnosed with CLL during the latter half of the study period, likely due to earlier detection of CLL, leading to a shorter follow-up time than anticipated. The short median follow-up time was also driven by the high mortality in this population, resulting in over half of the treated patients dying during follow-up.

Conclusions

This population-based study demonstrates excellent OS_i with FCR or BR for both U-CLL and M-CLL patients, indicating that patients who progress after first-line chemoimmunotherapy may be salvaged with second- or later-line treatments. In view of the long treatment-free period and the possibility of clinical cure for a substantial subgroup of M-CLL patients, intensive chemoimmunotherapy remains a valid treatment option and part of a personalized treatment landscape in CLL alongside targeted agents. Patients treated with chlorambucil-based regimens have a poor outcome; thus, improved supportive care and targeted treatment options, as seen in recent randomized controlled trials, are warranted for patients who are unfit for intensive chemoimmunotherapy.

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