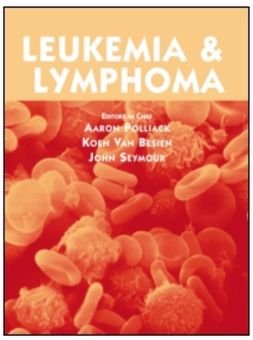

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ORIGINAL ARTICLE



# Survival improvement of patients with chronic lymphocytic leukemia (CLL) in routine care 1995–2017

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**ABSTRACT**

Seven hundred and twenty-four CLL-outpatients with a median age of 67 (35–92) were analyzed. Four hundred and twenty-seven (59%) were male, 297 (41%) female. At diagnosis 556 (77%) were in Binet stage A, 91 (13%) stage B and 36 (5%) stage C. Forty-six percent received treatment during the evaluation period. Treatment consisted of purine analogs in 38%, alkylating agents in 96%, chemoimmunotherapy with anti-CD20 monoclonal antibodies in 63%, ibrutinib in 9%, venetoclax in 1% and idelalisib in 3%. 3% received allogeneic hematopoietic stem cell transplantation. Overall survival (OS) according to Binet stage was: A 13.9 years (0.1–37.4), B 9.2 years (1.4–29.3) and C 7.9 years (0.5–19.4) respectively. Median OS from the start of therapy improved over time; 1995–2001: 5.8 years, 2002–2008: 6.1 years and 2009–2017: median not reached. Survival of patients with CLL has improved in routine care and was strongly related to active disease, disease stage, performance status and whether therapy included an anti-CD20 monoclonal antibody.

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## Introduction

Chronic lymphocytic leukemia (CLL) is classified as a lymphoproliferative disease with at least 5000 monoclonal B-lymphocytes per microliter in peripheral blood. The immunophenotype is characterized as CD19+, CD20+, CD23+ and CD5+ [1]. CLL is the most common indolent B-cell lymphoma with an incidence of 4–6/100 000 inhabitants per year in the western hemisphere [2]. Median age at diagnosis is around 70 years [2]. In Germany CLL is diagnosed early due to frequent routine blood checks by general practitioners who send their patients for further evaluations to hematologists. Survival in studies is strongly dependent on disease stage according to the classifications of Rai [3] and Binet [4]. In the early studies from 1981 patients with Binet stage A had a survival that was comparable to an age-matched population without CLL, stage B had a median survival of 84 months and Binet stage C of 24 months [4]. Back in 1981 the only treatment option available was chlorambucil with or without prednisone/prednisolone. In the meantime we have learned that CLL is a very inhomogeneous disease and that the course of the disease is influenced by a number of different prognostic factors. Genetically the 17p deletion/TP53 mutation and 11q deletion are associated with low response rates to standard CLL therapy and much shorter survival [5–7]. Fludarabine-containing regimens seem to have improved the outcome of patients with 11q deletion, but showed no improvement in patients with 17p deletion or TP53 mutation [5–7]. Experts in the field agree that patients with 17p deletion or TP53 mutation should be treated with ibrutinib, idelalisib plus rituximab or venetoclax and if suitable later by allogeneic hematopoietic stem cell transplantation (HSCT) [1]. Other factors conferring a shorter survival are an elevation of serum ß2-microglobulin, unmutated IGHV genes and age above 65 [8]. These prognostic factors have been put together to form the IPI-CLL prognostic scoring system, which helps us to estimate the risk of CLL progression into 'active disease' which should be treated [1,8]. The International Workshop on Chronic Lymphocytic Leukemia (iwCLL) defines criteria of active disease in patients who need therapy [1].

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During the last 20 years much progress has been made in CLL therapy. Since 2002 fludarabine and bendamustine have been shown to achieve higher response rates and longer progression-free survival (PFS) compared to chlorambucil [9,10]. The introduction of anti-CD20 monoclonal antibody therapy with rituximab has improved response rates, PFS and overall survival (OS) in CLL therapy [11]. Studies have shown that FCR (fludarabine + cyclophosphamide + rituximab) is more effective and achieves a slightly longer PFS compared to BR (bendamustine + rituximab) [12]. This goes along with an increased rate of neutropenia and infection, especially in patients older than 65 [12]. Thus experts agree that during FCR therapy and thereafter pneumocystis jirovecii prophylaxis with trimethoprim + sulfamethoxazole and anti-herpes virus prophylaxis with aciclovir are mandatory [1]. In elderly patients with comorbidities the combination of chlorambucil + obinutuzumab, a new class-II anti-CD20 antibody with increased antibody-dependent cell-mediated cytotoxicity (ADCC), showed a higher response rate and PFS when compared to chlorambucil + rituximab [13]. Ofatumumab, another anti-CD20 antibody, which binds to a different epitope of CD20 has shown high activity in combination with chlorambucil and bendamustine in the relapsed/refractory situation [14]. New drugs like the Bruton's tyrosine kinase inhibitor ibrutinib, the PI3K inhibitor idelalisib and the anti-BCL-2 agent venetoclax have shown high response rates in treatment naïve patients, but as well in the refractory and relapsed situation, even in patients with 17p deletion or TP53 mutation [15–17]. All three drugs have been licensed recently by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for first-line therapy of patients with 17p deletion or TP53 mutation. Ibrutinib has been licensed recently for first-line therapy of all patients with CLL. The only curative option for patients with CLL, especially for patients with 17p deletion or TP53 mutation, is allogeneic HSCT which is reserved for younger patients with few comorbidities and a suitable donor. Despite the fact that the best treatment for a CLL patient would be within a well-designed randomized controlled trial (RCT) only a minority of CLL patients are treated within a RCT for a number of reasons. As mentioned above CLL is an inhomogeneous disease and patients present with different comorbidities and wishes which preclude the majority of patients from enrollment into a RCT. Therefore it is difficult to judge whether progress made in RCT translates into a better survival in routine care. This was the reason for us to perform this routine care analysis in CLL patients. The questions we wanted to answer are the following:

1. Are the new therapeutic options which were developed during the last 20 years applied in routine care?
2. Has the overall survival in CLL patients changed during the last 20 years?

## Materials and methods

All patients with CLL who presented in a German hematology-oncology outpatient group practice and were treated by seven experienced hematologists (Praxis für Hämatologie und Onkologie Koblenz, Germany) between 06/1995–12/2017 were evaluated. Only data from patients who agreed upon data evaluation were captured. All relevant data were extracted by 3 experienced study nurses by going through each patient file, anonymized and then put into a database for statistical analyses with SPSS. Missing data were collected as far as possible by asking general practitioners and other relevant institutions. The study group collecting the data worked together in the same office environment. There were clear instructions in how to document to make sure the quality of data remains the same. Any arising problems in documenting correct data were addressed to the project manager. Written instructions on how to document were updated continuously. According to our ethics committee in Rhineland-Palatinate no formal ethics approval is necessary for data analysis of anonymized patient data where routine care is documented.

The following data were captured: Age, sex, stage, place of living, insurance status, profession, diagnostic procedures (blood count, immunophenotyping, cytogenetic and molecular genetic analyses, ß2-microglobulin, lymphocyte doubling time, lymph node extirpation, lymph node biopsy, bone marrow biopsy), treatment (number of lines, cytoreductive medication used, number of cycles), time to next therapy, hospitalizations (number, length, reason), overall survival (OS) defined as time from diagnosis to death or last contact, survival since therapy start defined as the time when the first therapy started to death or last contact, cause of death (CLL (infection, bleeding, kachexia, second cancer), comorbidities, other), place of death (at home, hospital, nursing home, other).

Diagnosis of CLL was made and active disease was defined as described by the International Working Group on CLL [1]. CLL stage was classified as described

by Binet et al [4]. The age-adjusted Charlson comorbidity index (aaCCI) was applied as described [18].

### Statistical analysis

Univariate analyses: statistical analyses were descriptive, specific hypotheses were not tested. Frequencies and statistical measures of central tendency were calculated, survival analyses were performed according to the method of Kaplan and Meier.

The following parameters were tested for prognostic significance concerning overall survival with the help of a Cox regression (proportional hazards regression): sex, age, stage, aaCCI, ECOG performance status and treatment with or without an anti-CD20 monoclonal antibody vs. no treatment. In the multivariate analysis were all variables included which showed statistical significance in the univariate log-rank tests.

Relative survival analysis was performed as the ratio of actual survival to expected survival. Expected survival was estimated using life tables stratified by age and sex of the Federal Statistical center of Germany according to the Ederer II method [19].

## Results

### Patients

724 patients with a median age of 67 (35–92) were diagnosed with CLL during the evaluation period. 427 (59%) were male, 297 (41%) were female. CLL stage according to Binet at diagnosis was A in 77%, B in 13% and C in 5%. In 6% stage was not available mostly due to external diagnoses. aaCCI at diagnosis was 2–3 in 19%, 4 in 27%, 5 in 24% and 6–11 in 31%. Median follow-up time was 7.1 (0–42) years. Patient characteristics according to the period of CLL diagnosis are shown in Table 1.

### Diagnostic procedures

CLL was diagnosed by blood lymphocyte immunophenotyping in 518 patients (72%). A bone marrow biopsy was performed in 189 patients (26%), lymph node extirpation or lymph node biopsy was done in 54 patients (7%). The importance of immunophenotyping for the diagnostic process increased over time. Immunophenotyping was used in 60% (1995–2001), 80% (2002–2008) and 88% (2009–2017) of patients. 248 (49%) of 504 patients diagnosed in 2001 or later received chromosomal analysis. A normal karyotype was present in 23% ($n = 56$), a deletion 13q in 44% ($n = 109$), a 11q deletion in 8% ($n = 20$) and a 17p deletion/TP53 mutation in 7% ($n = 18$). IgVH mutation status was captured in patients who were diagnosed in 2009 or later and was available in 182 patients. IgVH was mutated in 68/182 patients (37%) and unmutated in 114/182 patients (63%).

**Table 1.** Patient characteristics.

| | TOTAL | | Diagnosis 2001 or earlier | | Diagnosis 2002–2008 | | Diagnosis 2009–2017 | |
|---|---|---|---|---|---|---|---|---|
| Age at diagnosis | $N = 724$ | | $N = 258$ | | $N = 233$ | | $N = 233$ | |
| median/range | 67 years | 35–92 years | 65 years | 35–86 years | 68 years | 39–92 years | 70 years | 41–92 years |
| Age groups | *N* | % | *N* | % | *N* | % | *N* | % |
| <65 years | 286 | 39.5 | 122 | 47.3 | 84 | 36.1 | 80 | 34.3 |
| 65–69 years | 131 | 18.1 | 48 | 18.6 | 51 | 21.9 | 32 | 13.7 |
| 70–75 years | 129 | 17.8 | 50 | 19.4 | 39 | 16.7 | 40 | 17.2 |
| >75 years | 178 | 24.6 | 38 | 14.7 | 59 | 25.3 | 81 | 34.8 |
| Sex | $N = 724$ | | $N = 258$ | | $N = 233$ | | $N = 233$ | |
| male | 427 | 59.0 | 150 | 58.1 | 140 | 60.1 | 137 | 58.8 |
| female | 297 | 41.0 | 108 | 41.9 | 93 | 39.9 | 96 | 41.2 |
| Stage at diagnosis | $N = 724$ | | $N = 258$ | | $N = 233$ | | $N = 233$ | |
| Binet A | 556 | 76.8 | 197 | 76.4 | 184 | 79.0 | 175 | 75.1 |
| Binet B | 91 | 12.6 | 26 | 10.1 | 33 | 14.2 | 32 | 13.7 |
| Binet C | 36 | 5.0 | 13 | 5.0 | 9 | 3.9 | 14 | 6.0 |
| not available | 41 | 5.7 | 22 | 8.5 | 7 | 3.0 | 12 | 5.2 |
| ECOG performance status at diagnosis | $N = 442$ | | $N = 81$ | | $N = 157$ | | $N = 204$ | |
| ECOG ≤1 | 395 | 89.4 | 72 | 88.9 | 143 | 91.1 | 180 | 88.2 |
| ECOG ≥2 | 47 | 10.6 | 9 | 11.1 | 14 | 8.9 | 24 | 11.8 |
| Age adjusted Charlson Comorbidity Index (aaCCI) | $N = 683$ | | $N = 232$ | | $N = 225$ | | $N = 226$ | |
| aaCCI 2–3 | 132 | 19.3 | 54 | 23.3 | 39 | 17.3 | 39 | 17.3 |
| aaCCI 4 | 180 | 26.4 | 68 | 29.3 | 59 | 26.2 | 53 | 23.5 |
| aaCCI 5 | 160 | 23.4 | 53 | 22.8 | 60 | 26.7 | 47 | 20.8 |
| aaCCI 6–11 | 211 | 30.9 | 57 | 24.6 | 67 | 29.8 | 87 | 38.5 |

### Therapy

Of 724 patients 335 (46%) needed therapy. Therapy consisted of alkylating agents (chlorambucil, bendamustine, cyclophosphamide) in 96%, purine analogs (fludarabine, pentostatine) in 38%, chemoimmunotherapy using an anti-CD20 monoclonal antibody (rituximab, ofatumumab, obinutuzumab) in 63%, ibrutinib in 9%, idelalisib + rituximab in 3% and venetoclax in 1% of the treated patients. 10 patients (3%) received an allogeneic HCST, mostly in 4$^{th}$ line or later. The distribution of first line, second line and third-line therapies according to the period of CLL diagnosis is depicted in Table 2. Chemotherapeutic substances most frequently used were bendamustine in 441/1 259 therapies (35%), chlorambucil in 274/1 259 therapies (22%) and fludarabine in 163/1 259 therapies (13%). Anti-CD20 monoclonal antibodies used in the order of frequency were rituximab in 457/1 259 therapies (36%), obinutuzumab in 17/1 259 therapies (1%) and ofatumumab in 14/1 259 therapies (1%). Patients received a median of 2 therapy lines (1–13). The median time on therapy was 8 months (less than 1 month–249 months (intermittent chlorambucil)). Median time to first-line therapy was 25.9 (0–408) months.

### Hospitalizations

Four hundred and fifty-one patients (62%) needed hospital treatment for a variety of reasons. Hospital admission was caused by comorbidities in 940 hospitalizations (72%), CLL-related symptoms that required hospitalization in 200 (15%), inpatient CLL therapies in 63 (5%), side effects of the outpatient therapy in 43 (3%) and by other reasons in 62 cases (5%). Median hospital admissions were 2 (1–20) and median cumulative length of hospital stays was 23 days (1–407).

### Survival

Five- and 10-year relative survival (RS) of the whole cohort was 98% and 85% respectively. Five- and 10-year RS was not different between men and women (98%/85% versus 97%/84%).

Median OS according to Binet stage A, B, C was 13.9 years (0.1–37.4+), 9.2 years (0.1–29.3) and 7.9 years (0.5–19.4) respectively ($p<.001$). OS was strongly dependent on the aaCCI: patients with a score of 2–3 had a median survival of 23.7 years, patients with a score of 4 lived 14.2 years, patients with a score of 5 lived 59.7 years and patients with a score of >5 lived 7.2 years only. This was statistically significant with a $p$ value of <.001. Median OS according to the period of CLL diagnosis was 12.3 years (0.7–41.8) for patients diagnosed in 2001 or earlier and 13.3 years (0.1–15.5+) for patients diagnosed between 2002 and 2008. The median was not reached in the group who was diagnosed between 2009 and 2017 ($p = .335$).

Median OS from the start of therapy improved over time; 1995–2001: 5.8 years, 2002–2008: 6.1 years and 2009–2017: not reached ($p = .051$) (Figure 1). Chemoimmunotherapy with an anti-CD20 monoclonal antibody had a significant impact on the length of survival since the start of therapy. Patients receiving chemoimmunotherapy lived 8.9 years (age at therapy start 70 years or younger) and 5.5 years (71 years or older) respectively compared to 4.7 years (70 years or younger) and 3.6 years (71 years or older) in patients without chemoimmunotherapy ($p < .001$) (Figure 2).

Multivariate analysis revealed that the presence of an active disease and accordingly a higher Binet stage had a dominant influence on survival and that all other variables were of secondary importance: Binet B vs. Binet A hazard ratio (HR)=2.13 (95% confidence interval (CI)) = 1.31–3.46 and Binet C vs. Binet A HR = 3.74 (95% CI = 1.88–7.46) (Table 3). Known predictors for a shorter survival like a high IPI-CLL score could not be used for multivariate analysis due to missing data for 17p deletion/TP53 mutation, IGVH mutational status and ß2-microglobulin in the majority of patients.

### Death

During the observation period 313 patients have died (43%). Hundred and twelve patients (36%) died of CLL and CLL-related complications, 82 patients (26%) died due to comorbidities, 2 patients (1%) died of other causes, in 3 patients (1%) death was therapy associated and in 114 patients (36%) the cause of death could not be determined. In patients with active disease 86 patients (43%) died due to CLL and 40 (20%) due to comorbidities. In patients who never needed any CLL therapy 11 (10%) formally died due to CLL (6 due to infections and 5 due to second cancer). Forty-two (37%) died due to comorbidities.

## Discussion

### Treatment

During the last 20 years a variety of new treatment options have been developed for CLL patients. We could show that the combination of bendamustine + mitoxantrone + rituximab is especially suitable for elderly outpatients with comorbidities in the relapsed situation [20] and that retherapy with this

**Table 2.** 1st line, 2nd line and 3rd line therapies according to the period of CLL diagnosis.

| | 1st line | | | | | | | | 2nd line | | | | | | | | 3rd line | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TOTAL | | Diagnosis 2001 or earlier | | Diagnosis 2002–2008 | | Diagnosis 2009–2017 | | TOTAL | | Diagnosis 2001 or earlier | | Diagnosis 2002–2008 | | Diagnosis 2009–2017 | | TOTAL | | Diagnosis 2001 or earlier | | Diagnosis 2002–2008 | | Diagnosis 2009–2017 | |
| | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | N | % |
| bendamustine | 14 | 4.2 | 2 | 1.3 | 5 | 4.4 | 7 | 9.6 | 14 | 6.6 | 5 | 4.3 | 8 | 11.9 | 1 | 3.3 | 7 | 5.4 | 4 | 5.2 | 2 | 4.7 | 1 | 10.0 |
| bendamustine + mitoxantrone (BM) | 6 | 1.8 | 3 | 2.0 | 3 | 2.7 | 0 | 0.0 | 48 | 22.5 | 40 | 34.5 | 8 | 11.9 | 0 | 0.0 | 13 | 10.0 | 11 | 14.3 | 2 | 4.7 | 0 | 0.0 |
| bendamustine + rituximab (BR) | 51 | 15.2 | 6 | 4.0 | 25 | 22.1 | 20 | 27.4 | 22 | 10.3 | 7 | 6.0 | 12 | 17.9 | 3 | 10.0 | 11 | 8.5 | 4 | 5.2 | 5 | 11.6 | 2 | 20.0 |
| bendamustine + mitoxantrone + rituximab (BMR) | 14 | 4.2 | 1 | 0.7 | 6 | 5.3 | 7 | 9.6 | 33 | 15.5 | 18 | 15.5 | 13 | 19.4 | 2 | 6.7 | 34 | 26.2 | 23 | 29.9 | 10 | 23.3 | 1 | 10.0 |
| chlorambucil | 149 | 44.5 | 114 | 76.5 | 34 | 30.1 | 1 | 1.4 | 8 | 3.8 | 2 | 1.7 | 4 | 6.0 | 2 | 6.7 | 5 | 3.8 | 4 | 5.2 | 1 | 2.3 | 0 | 0.0 |
| chlorambucil + obinutuzumab | 11 | 3.3 | 0 | 0.0 | 4 | 3.5 | 7 | 9.6 | 2 | 0.9 | 0 | 0.0 | 0 | 0.0 | 2 | 6.7 | 1 | 0.8 | 0 | 0.0 | 1 | 2.3 | 0 | 0.0 |
| cyclophosphamide | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 3 | 1.4 | 1 | 0.9 | 2 | 3.0 | 0 | 0.0 | 2 | 1.5 | 2 | 2.6 | 0 | 0.0 | 0 | 0.0 |
| cyclophosphamide + vincristine + prednisone (COP) | 3 | 0.9 | 2 | 1.3 | 1 | 0.9 | 0 | 0.0 | 5 | 2.3 | 5 | 4.3 | 0 | 0.0 | 0 | 0.0 | 2 | 1.5 | 2 | 2.6 | 0 | 0.0 | 0 | 0.0 |
| CHOP | 1 | 0.3 | 1 | 0.7 | 0 | 0.0 | 0 | 0.0 | 1 | 0.5 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 | 3 | 2.3 | 3 | 3.9 | 0 | 0.0 | 0 | 0.0 |
| R-CHOP | 5 | 1.5 | 1 | 0.7 | 0 | 0.0 | 4 | 5.5 | 4 | 1.9 | 1 | 0.9 | 2 | 3.0 | 1 | 3.3 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| fludarabine | 7 | 2.1 | 5 | 3.4 | 2 | 1.8 | 0 | 0.0 | 20 | 9.4 | 20 | 17.2 | 0 | 0.0 | 0 | 0.0 | 4 | 3.1 | 3 | 3.9 | 0 | 0.0 | 1 | 10.0 |
| fludarabine + cyclophosphamide (FC) | 23 | 6.9 | 6 | 4.0 | 16 | 14.2 | 1 | 1.4 | 3 | 1.4 | 2 | 1.7 | 1 | 1.5 | 0 | 0.0 | 2 | 1.5 | 0 | 0.0 | 2 | 4.7 | 0 | 0.0 |
| fludarabine + cyclophosphamide + rituximab (FCR) | 31 | 9.3 | 4 | 2.7 | 13 | 11.5 | 14 | 19.2 | 10 | 4.7 | 2 | 1.7 | 5 | 7.5 | 3 | 10.0 | 12 | 9.2 | 8 | 10.4 | 4 | 9.3 | 0 | 0.0 |
| ibrutinib | 4 | 1.2 | 0 | 0.0 | 0 | 0.0 | 4 | 5.5 | 5 | 2.3 | 1 | 0.9 | 4 | 6.0 | 0 | 0.0 | 4 | 3.1 | 2 | 2.6 | 1 | 2.3 | 1 | 10.0 |
| idelalisib + rituximab | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 3 | 1.4 | 1 | 0.9 | 1 | 1.5 | 1 | 3.3 | 1 | 0.8 | 0 | 0.0 | 0 | 0.0 | 1 | 10.0 |
| rituximab | 4 | 1.2 | 0 | 0.0 | 1 | 0.9 | 3 | 4.1 | 11 | 5.2 | 1 | 0.9 | 2 | 3.0 | 8 | 26.7 | 20 | 15.4 | 9 | 11.7 | 9 | 20.9 | 2 | 20.0 |
| alemtuzumab | 2 | 0.6 | 1 | 0.7 | 0 | 0.0 | 1 | 1.4 | 1 | 0.5 | 0 | 0.0 | 0 | 0.0 | 1 | 3.3 | 2 | 1.5 | 0 | 0.0 | 1 | 2.3 | 1 | 10.0 |
| prednison/prednisolone | 1 | 0.3 | 0 | 0.0 | 0 | 0.0 | 1 | 1.4 | 2 | 0.9 | 1 | 0.9 | 1 | 1.5 | 0 | 0.0 | 1 | 0.8 | 0 | 0.0 | 1 | 2.3 | 0 | 0.0 |
| others | 9 | 2.7 | 3 | 2.0 | 3 | 2.7 | 3 | 4.1 | 18 | 8.5 | 8 | 6.9 | 4 | 6.0 | 6 | 20.0 | 6 | 4.6 | 2 | 2.6 | 4 | 9.3 | 0 | 0.0 |
| SUM | 335 | 100 | 149 | 100 | 113 | 100 | 73 | 100 | 213 | 100 | 116 | 100 | 67 | 100 | 30 | 100 | 130 | 100 | 77 | 100 | 43 | 100 | 10 | 100 |

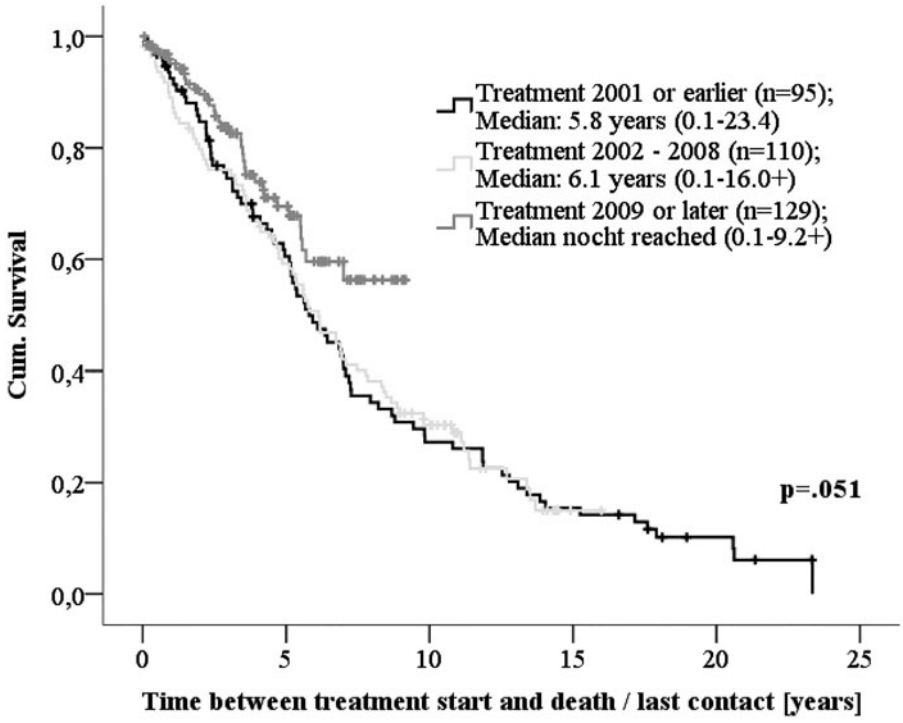


**Figure 1.** Overall survival, defined as time between treatment start and death/last contact in years, for patients who had CLL treatment 2001 or earlier, between 2002 and 2008 or between 2009 and 2017.

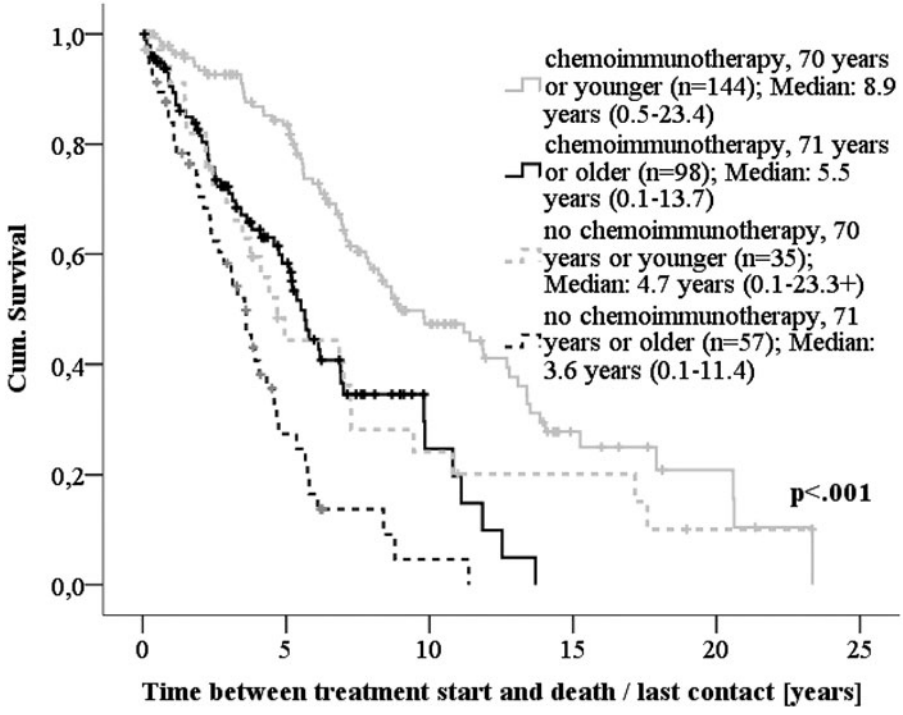


**Figure 2.** Overall survival, defined as time between treatment start and death/last contact in years, for patients with chemoimmunotherapy with an anti-CD20 monoclonal antibody and for patients without chemoimmunotherapy.

combination is effective and tolerable [21]. It has been shown that BR was the most frequently used regimen for first and second-line therapy in routine care in Germany between 2009–2013 [22]. The CLL-11 trial proved the combination of chlorambucil + obinutuzumab (CO) more effective concerning response rate and PFS compared to chlorambucil + rituximab (CR) in elderly patients with significant

**Table 3.** Output of the Cox regression model.

| | Estimates | | | | | |
|---|---|---|---|---|---|---|
| Variables | beta | standard error | *p*-value | hazard ratio | 95% confidence interval | |
| Age | 0.052 | 0.015 | 0.001 | 1.054 | 1.023 | 1.086 |
| Sex | 0.201 | 0.198 | 0.309 | 1.223 | 0.830 | 1.802 |
| Binet A | | | <0.001 | | | |
| Binet B | 0.756 | 0.247 | 0.002 | 2.130 | 1.312 | 3.460 |
| Binet C | 1.320 | 0.352 | <0.001 | 3.743 | 1.878 | 7.461 |
| aaCCI | 0.083 | 0.097 | 0.388 | 1.087 | 0.899 | 1.314 |
| ECOG 0 | | | <0.001 | | | |
| ECOG 1 | 0.152 | 0.220 | 0.490 | 1.164 | 0.756 | 1.793 |
| ECOG 2-3 | 1.098 | 0.254 | <0.001 | 2.998 | 1.822 | 4.932 |
| No CLL therapy | | | 0.040 | | | |
| CLL therapy without anti-CD20 antibody | 0.686 | 0.285 | 0.016 | 1.986 | 1.137 | 3.469 |
| CLL therapy including anti-CD20 antibody | 0.438 | 0.229 | 0.056 | 1.550 | 0.990 | 2.428 |

comorbidities with a CIRS score of >6 [13,23]. Due to the results of the CLL-11 study it has been licensed for elderly patients with significant comorbidities and a CIRS score above 6.

Very recently new data concerning therapy effectiveness and PFS of ibrutinib have been published. The iLLUMINATE-trial could show that ibrutinib + obinutuzumab produces a significant longer PFS compared to chlorambucil + obinutuzumab [24]. In older patients ibrutinib + rituximab has shown a longer PFS compared to bendamustine + rituximab as initial therapy [25]. Recently data of the E1912-trial have been presented at the ASH-meeting 2018 showing that first line ibrutinib-based therapy was more effective than FCR in younger patients [26]. A recently published phase III study comparing bendamustine + rituximab with venetoclax + rituximab in relapsed/refractory CLL showed significantly higher rates of progression-free survival in patients receiving venetoclax + rituximab [27].

In our retrospective analysis we could show that 54% of the patients never needed any therapy and that in patients with active disease all new therapeutic options are used in routine care. The majority of patients (72%) with active disease received chemoimmunotherapy with an anti-CD20 monoclonal antibody.

First-line therapy consisted of chlorambucil in 77% of patients diagnosed 2001 or earlier. In patients diagnosed between 2009 and 2019 only 1% received chlorambucil as first-line treatment. BR/BMR was applied in 19% and FCR in 9% of all first-line therapies. As 2nd line treatment BM/B was used most frequently (29%), followed by BMR/BR (26%), fludarabine (9%) and rituximab (5%). Highly pretreated refractory/relapsed patients and patients with 17p deletion/TP53 mutation were treated with ibrutinib (9%). 1% of patients received venetoclax and 3% an allogeneic HSCT. 18% of all patients were treated within a RCT. Especially for patients with a low-performance score or who have impaired organ function as well as for patients with TP53 deletion/mutation ibrutinib, idelalisib + rituximab and venetoclax are valuable new treatment options. For patients whose CLL has lost CD20-expression ibrutinib and venetoclax are therapies of choice.

## *Survival*

Survival of CLL patients who were treated in RCT has improved with chemoimmunotherapies during the last 20 years [28–30] and probably will improve in subgroups with 17p deletion/TP53 mutation and chemoimmunotherapy resistant patients with ibrutinib, idelalisib + rituximab and venetoclax + rituximab therapy, because median survival in these patients was very short before the introduction of these new treatment modalities into the clinic. A number of registry data and single center studies from Scandinavia, Germany, Spain and the US have reported improved survival for CLL patients during the last decades using large patient numbers [31–35]. 5-year relative survival was 73–82% and 10-year relative survival was 53–64% [31–33]. Between 1997–2011 five- and 10-year RS estimates in Germany have been found to be 80.2% and 59.5% respectively [33]. In our group of patients we found a 5-year RS of 98% and a 10-year survival of 85%. Disease specific survival according to Binet stage was 13 years for Binet A, 9.2 years for Binet B and 8.6 years for Binet C which is considerably longer in Binet B- and Binet C-patients as described originally in 1981 [4]. When we analyzed different treatment cohorts (1995–2001 versus 2002–2008 versus 2009–2017) we found a continuing rise in survival probability over time (Figure 1). Concerning the influence of treatment modalities on survival we could show that chemoimmunotherapy with an anti-CD20

monoclonal antibody is correlated to a significant longer survival (7.8 years for chemoimmunotherapy versus 3.8 years for no therapy with an anti-CD20 monoclonal antibody). We conclude that therapy with an anti-CD20 monoclonal antibody is one reason for improved survival in our cohort. This is in accordance with data from the German CLL Study Group and other groups showing that treatment with an anti-CD20 antibody is associated with a better overall survival [28–30]. Recently a nation-wide real-world study from Sweden reported no survival improvement between 2007–2013 looking at 1053 patients receiving first-line therapy [36]. First-line therapy consisted of chlorambucil in 39% of patients without an anti-CD20-antibody in 95%. Less than 50% of the patients received an anti-CD20-antibody and only 6% bendamustine [36]. A Spanish group reported improved survival in CLL patients younger than 70 years in Binet stage B and C between 1995–2004 suggesting that newer treatments are changing the prognosis of CLL [34]. This is in line with our findings.

Our routine care patient cohort had a median age at diagnosis of 67 (35–92), which is comparable to data from Spain [34], and a median age at first treatment of 70 (35–92). Median age at start of first-line therapy was 71 (31–96) in a Swedish registry [36] and 68 (22–99) in an American cohort study [37]. The age of our patient population, therefore, seems to be in a range comparable to other real-world data analyzes.

Concerning comorbidities it has been shown by different groups that a higher number of comorbidities is correlated to a shorter survival [38,39]. It has been postulated in RCT that the main cause of death in patients with more comorbidities leads to less effective CLL therapy resulting in a rise in CLL-associated deaths [38,39]. This may be true in CLL patients with active disease who need therapy. In our patient group where comorbidities and causes of death were known in 94% and 66% of patients respectively, we could show that a high number of comorbidities according to the aaCCI is a strong prognostic factor for shorter survival for all CLL patients irrespective if they needed therapy or not. When we compared the cause of death in patients with active disease needing therapy with patients without the need for CLL therapy, we found CLL as the major cause of death in patients needing therapy but comorbidities in patients where CLL was never treated. In accordance with reports from RCT we confirm CLL as the major cause of death in routine care CLL patients who need cytoreductive therapy (43% CLL, 20% comorbidities) [38,39]. New drugs like ibrutinib, idelalisib and venetoclax will improve our ability to control CLL in all patients but especially in patients with comorbidities. This will probably lead to improved survival in this cohort of patients which is difficult to treat.

In summary, our data suggest that results from randomized controlled trials can be transferred into real world CLL-patient care and that the new therapeutic options available (anti-CD20-antibodies, tyrosine kinase inhibitors and BCL2-inhibitors) improve survival in routine care.

### *Strengths and weaknesses*

To the best of our knowledge, this is the first report of a large number of consecutive CLL patients who were treated as outpatients in a community-based hematology-oncology group practice receiving routine care during the last 22 years in Germany.

The data set is complete concerning demographic data, stage, comorbidities, therapy and in 66% cause of death. All consecutive patients were documented by three experienced study nurses.

Weaknesses are that the study was retrospective and monocentric.

## Conclusions

1. Survival of CLL patients who receive their treatment in routine care has improved during the last 22 years.
2. The reason for improved survival is improved cytoreductive therapy, mainly due to the usage of anti-CD20 monoclonal antibodies.
3. All new diagnostic and therapeutic options are used in routine care.
4. In the present analysis, major prognostic factors conferring a shorter survival are active disease, advanced stage at diagnosis, reduced performance status and therapy without an anti-CD20 monoclonal antibody.

## Disclosure statement

All authors declare that there are no competing financial interests in relation to this work.

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