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RESEARCH ARTICLE

A decade of chronic lymphocytic leukaemia therapy in Germany: Real-world treatment patterns and outcomes (2010–2022)

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Abstract

Pharmacotherapy options for chronic lymphocytic leukaemia (CLL) have expanded significantly in recent years. These options include chemotherapy, chemoimmunotherapy and signalling pathway inhibitors. A notable shift in the treatment landscape began with the widespread adoption of ibrutinib in 2016. This analysis of claims data focuses on understanding how the use of novel therapies has evolved in clinical practice over the past decade in Germany. Anonymized claims data (2010–2022) from German statutory health insurance was used, covering patient demographics, treatments, and prescriptions. The study population included patients with two confirmed CLL diagnoses. Treatment patterns were analysed, and survival outcomes were compared using time-to-event analyses. In the analysed cohort of 2983 incident CLL patients, 1041 started first-line therapy between 2011 and 2022, with a median duration of 18 months from diagnosis to the first prescription. Chemoimmunotherapy, the predominant 1L therapy until 2019, decreased significantly, while targeted therapy usage increased from 3% in 2015 to 77% in 2022. Targeted therapies became dominant in patients receiving treatment for relapsed or refractory disease after 2016. Median treatment durations were: 122 days for chemo, 176 days for chemo-immuno, and 373 days for targeted therapy. The overall survival for patients diagnosed in or after 2016 was significantly better (hazard ratio 0.56, 95% confidence interval, 0.44–0.69)). The adoption of targeted therapies like ibrutinib and venetoclax has transformed CLL treatment in Germany, leading to improved patient outcomes. Additionally, we demonstrate successful adherence to evolving clinical guidelines.

KEYWORDS

chronic lymphocytic leukaemia, claims data analysis, epidemiology, Germany, real-world data analysis, treatment pattern

1 | INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is the most common hematologic malignancy. It is an indolent lymphoproliferative disease of malignant B-cells. With a few exceptions (e.g. following allogeneic stem cell transplantation), CLL is considered incurable. Therefore, CLL patients need lifelong care and multiple therapy episodes, typically alternating with therapy-free intervals of varying duration. After achieving remission or refractory disease (RF), relapses can still be successfully treated with alternative therapy regimens, including chemoimmunotherapy, signalling pathway inhibitors, allogeneic transplantation, and more recently, chimeric antigen receptor T-cells as an off-label treatment. This diverse array of treatment options highlights the remarkable progress achieved over the past decade [1–3]. Chemotherapy had been the only therapy option for decades, and cytotoxic drugs such as purine analogues (e.g. fludarabine) or alkylating agents (e.g. chlorambucil, cyclophosphamide or bendamustine) have been widely used as monotherapy or in combination [4, 5]. Chemoimmunotherapy—a combination of chemotherapy with a CD20 monoclonal antibody (e.g. rituximab and obinutuzumab)—was introduced more than 20 years ago and has significantly increased survival compared to chemotherapy alone [6–10]. More recently, signalling pathway inhibitors such as ibrutinib (BTK-inhibitor), idelalisib (PI3K-inhibitor), and venetoclax (BCL2-inhibitor) have been approved for the treatment of CLL, also in combination with CD20 antibodies [11–14].

The recent and rapid changes in CLL treatment have necessitated multiple updates to the guidelines of the German Society of Haematology and Medical Oncology, resulting in a total of seven revisions since 2010 [15]. These clinical guidelines aim to enhance the quality of patient care, prioritizing the enhancement of health outcomes and maintaining consistency in care delivery. Deviating from guidelines can result in practices that are not beneficial to patients and the misallocation of healthcare resources [16]. Understanding how guidelines are applied in real-world settings is crucial for evaluating their effectiveness.

Real-world data analysis, an accepted tool for estimating epidemiological parameters and identifying changes in treatment patterns, provides valuable insights into the practical implementation of guidelines [9, 10, 17–23]. In Germany, healthcare claims data collected by statutory healthcare insurance providers has been instrumental in epidemiological research for over two decades [24–26]. This study analyses CLL treatment patterns from 2010 to 2022 utilizing claims data, tracking the adaptation to evolving therapy recommendations. Furthermore, we explore whether there has been a discernible shift in survival outcomes, particularly following the extension of ibrutinib as a first-line (1L) treatment for CLL in 2016.

2 | METHODS

2.1 | Data source

Anonymized claims data (2010–2022) from 19 German statutory health insurance (SHI) providers was provided by GWQ ServicePlus AG, a joint venture of medium-sized health insurers in Germany. The dataset comprised information on approximately 6 million people. The routinely collected data consisted of demographic data, pharmaceutical dispenses, documented diagnoses and services provided in both ambulatory and statutory care. However, laboratory or clinical parameters were not part of the dataset.

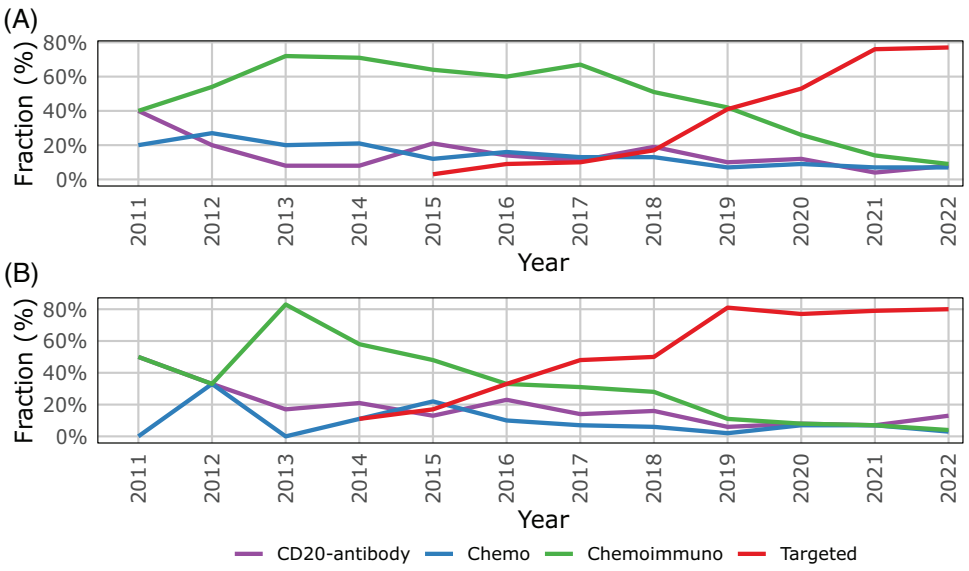

FIGURE 1 Fraction of the four types of pharmaceutical CLL therapies were examined: CD20-antibody monotherapy (purple), chemotherapy (blue), chemoimmunotherapy (green), and targeted therapy (red), distinguishing between (A) 1L and (B) RF treatments.

2.2 | Study population

The study included patients with a confirmed CLL diagnosis (ICD-10-GM code: C91.1), identified either as a primary or secondary inpatient diagnosis or as an outpatient diagnosis by a haematologist, oncologist, internal medicine specialist or laboratory medicine specialist. Eligibility for analysis required patients to have consistent diagnoses in two consecutive quarters [27] and a minimum of four quarters of insurance coverage prior to their initial CLL diagnosis. Exclusion criteria included incomplete demographic data (sex and age) and less than one year of follow-up post-diagnosis.

2.3 | Treatment

Prescriptions related to CLL treatment were selected [15, 28], and prescriptions that occurred only once per patient were excluded. The initiation of 1L therapy was indicated by the initial relevant prescription and extended until a 6-week period without any new prescriptions. Subsequent prescriptions indicated the start of RF therapy. Identical consecutive therapy regimens were combined into a single line. For our analysis in Figure 1 as well as the treatment duration, we only included therapy regimens that appeared in more than five patients. For the analysis of treatment duration, only completed treatments without recent prescriptions in the last quarter were included.

2.4 | Statistical analysis

The overall survival (OS) of patients starting CLL treatment before and in/after 2016 was measured with time-to-event analyses. Specifically, the duration from a patient's initial CLL diagnosis until death was observed. Kaplan-Meier curves with log-rank tests were used to compare patient groups. To acquire the hazard ratios (HRs) of death along with their corresponding 95% confidence intervals (CIs), a multivariate Cox proportional hazard model was employed. This model was adjusted for age at diagnosis, sex, and the Charlson Comorbidity Index (based on diagnoses from the previous four quarters prior to the initial diagnosis).

All data processing and analysis were done on the software R-Studio 2022.02.0 using R version 4.1.3.

3 | RESULTS

3.1 | Population characteristics

Among the dataset of 6 million individuals, there were 2977 diagnosed CLL patients (1850 males and 1127 females), with 1040 (684 males and 356 females) initiating 1L therapy between 2011 and 2022. The median time to the first prescription after the initial diagnosis for patients undergoing therapy was 18 months. RF therapy was initiated in 341 patients.

3.2 | Treatment patterns

When analysing CLL treatment changes over the last decade, four types were examined: CD20-antibody monotherapy, chemotherapy, chemoimmunotherapy, and targeted therapy distinguishing between 1L and RF therapy. For 1L therapy, chemoimmunotherapy was dominant from 2011 to 2019, reaching its peak at 72% in 2013, but subsequently declined to 9% by 2022. Targeted therapy in 1L therapy rose from 3% in 2015 to 77% in 2022. CD20-monotherapy and chemotherapy, initially prevalent, dropped to 8% and 7%, respectively, by 2022 (Figure 1A). For RF therapy, chemoimmunotherapy, which was extensively prescribed until 2016, reached its peak at 83% in 2013 but decreased to 4% by 2022. The usage of chemo- and CD20-monotherapy fluctuated, settling at 3% and 13% respectively in 2022. Targeted therapy in RF therapy, starting at 11% in 2014, matched chemoimmunotherapy by 2016, peaked at 81% in 2019, and subsequently stabilized (Figure 1B).

Next, the top five 1L and RF regimes for CLL before and after 2016, when the first targeted therapy Ibrutinib (Ibr) was approved for 1L therapy, were analysed. For 1L therapy, bendamustine/bendamustine + rituximab (B/BR) usage grew between 2010 and 2015 and remained the predominant therapy option, while Rituximab (R) and other therapies like fludarabine + cyclophosphamide + rituximab (FCR) and chlorambucil (Ch) showed varying trends (Figure 2A). Post-2016, BR initially led, with Ibr and venetoclax + obinutuzumab (V+O) gaining prominence being the most prescribed in 2019 (47%) and 2022 (58%), respectively (Figure 2B). For RF therapy, R was initially prevalent in 2011, followed by a rise in B/BR and the introduction of Ibr and idelalisib + rituximab (Id+R) in 2014 (Figure 2C). Post-2016, Ibr was the most prescribed therapy until being overtaken by venetoclax mono- or venetoclax + rituximab combination therapies (V/V+R) in 2021, with other therapies showing variable usage (Figure 2D).

3.3 | Duration of treatment

The median duration of treatment was 154.5 days (interquartile range [IQR] 163.5 days) for CD20-mono therapy, 122 days (IQR 289 days) for chemotherapy, 176 days (IQR 41 days) for chemoimmunotherapy and 373 days (IQR 485.75) for targeted therapy (Table 1). The two most prescribed regimes within targeted therapy were Ibr (median duration 630 days, IQR 838.25 days) and V+O (median duration 308 days, IQR 176.5 days) (Table 1).

3.4 | Overall-survival

The median OS after the first diagnosis for CLL patients was not reached within the observation period. For those receiving 1L therapy,

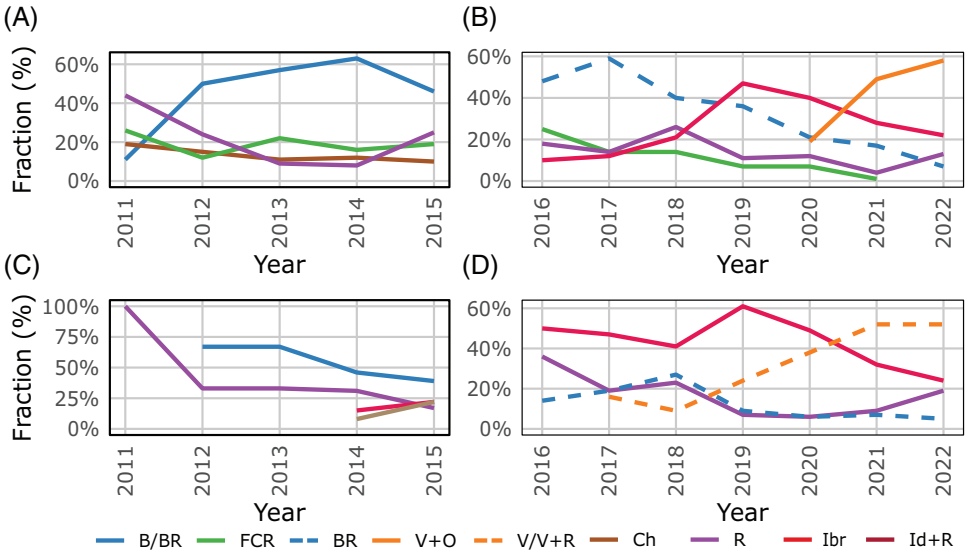

FIGURE 2 Fraction of the top 5 regimes for (A) 2011–2015 1L, (B) 2016–2022 1L, (C) 2011–2015 RF and (D) 2016–2022 RF. 1L: first-line therapy; RF: refractory therapy; B/BR: bendamustine / bendamustine + rituximab; FCR: fludarabine + cyclophosphamide + rituximab; V+O: venetoclax + obinutuzumab; V+R: venetoclax + rituximab; Ch: chlorambucil; Ibr: ibrutinib, Id+R: idelalisib + rituximab.

TABLE 1 Treatment duration of first-line therapy.

Type of treatment	Median (days)	IQR	*n*
CD20-mono	154.5	163.5	126
Chemo	122	289	124
Chemoimmuno	176	41	429
Targeted	373	485.75	218
Ibr	630	838.25	92
V+O	308	176.5	67

Abbreviations: IQR, interquartile range; Ibr, Ibrutinib; V+O, Venetoclax + Obinutuzumab.

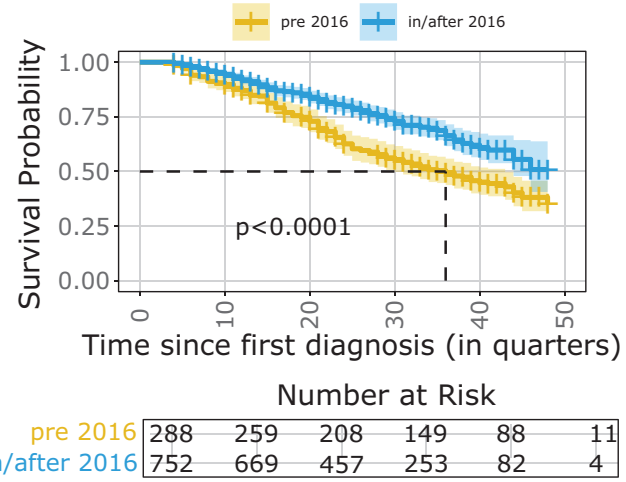

FIGURE 3 Overall survival from 1. Diagnosis for 1040 CLL patients starting 1L treatment before 2016 or in/after 2016.

the median OS was 11 years, 10 years for males while the median OS was not reached for females. To assess changes in CLL therapy outcomes after introducing targeted therapy in 1L therapy, OS was calculated based on the year of diagnosis stratified by year of first therapy: before 2016 ($n = 289$) versus 2016 or later ($n = 752$) (Figure 3). The median OS for patients diagnosed before 2016 was 9 years. In the group diagnosed in or after 2016, the median OS had not been reached at the time of analysis ($p < 0.001$). The OS for patients diagnosed in or after 2016 was significantly better (HR 0.56 [95%-CI, 0.44–0.69]).

4 | DISCUSSION

The treatment landscape for CLL in Germany has significantly changed over the past decade, marked by key pharmaceutical approvals. Assessing the treatment landscape and its evolution, especially concerning guidelines, is crucial.

Following its approval in December 2010, B/BR became the primary treatment for CLL from 2013 to 2016/2017. Subsequently, its prominence later declined coinciding with the rise of targeted therapies, starting with the approval of ibrutinib in 2014. Ibrutinib was initially approved for patients with del(17p13) or TP53 mutations. After the expansion to 1L therapy of all CLL patients in 2016, ibrutinib emerged as the primary choice by 2019. The introduction of venetoclax, a BCL2-inhibitor, in December 2016, marked another evolution in CLL treatment. Venetoclax rapidly became part of treatment guidelines, initially in 2017 for RF therapy in patients with del(17p13) or TP53 mutations, and by 2019 for all RF patients. With its expanded authorization for use in untreated patients, particularly in combination with obinutuzumab, venetoclax surpassed ibrutinib by 2021 in both 1L and RF therapy. The rapid adoption of new targeted therapies has greatly expanded treatment choices for CLL. These trends closely follow German guidelines from 2014–2023, indicating strong adherence to the

guidelines [15]. One deviation from guideline adherence was observed in the utilization of CD20 antibody monotherapies, particularly rituximab, which was employed in approximately 15% of 1L therapies on average [28]. The specific reasons for these rituximab prescriptions, whether for autoimmune cytopenias or CLL therapy, remain unclear, echoing a challenge highlighted by Seymour *et al*. in their analysis of the SEER data [21].

Other studies based on real-world evidence reported similar results for Europe and North America with a few notable differences [17–23]. In a study by Huang et al., reported for British Columbia, Canada, the most prevalent 1L therapy between 2014 and 2015 was reported to be fludarabine + rituximab (54.3%), a combination that did not rank among the top five in this analysis [18]. They further reported an ibrutinib usage of 18.7% in 1L therapy in 2016, suggesting a significantly faster adaptation compared to the 10% usage we reported for that year [18]. Ranti *et al.* analysed a Finnish cohort of CLL patients. During the period from 2005 to 2013, chlorambucil-based regimens were the leading 1L therapies, administered to nearly 42% of patients, while FC or FCR was used for 27%. However, in the subsequent period from 2014 to 2019, the increased adoption of B/BR, reaching approximately 27%, aligns more closely with our findings and may suggest a slower adaptation of bendamustine-based therapies [17]. Similarly, Sylvan *et al.* demonstrated a B/BR utilization rate of only 9% in 1L therapy for a Swedish cohort between 2010 and 2013 [23]. The quicker adoption of bendamustine-based regimens in Germany may be attributed to the extensive experience German oncologists have had with bendamustine since the 1960s, prior to its CLL treatment approval [29].

A primary distinction among chemo-, chemoimmuno-, and targeted therapy lies in the treatment duration. Chemo and chemoimmunotherapy typically require six 28-day cycles. In contrast, targeted therapy may extend over 12 cycles, such as V+O [13, 15], or continue until disease progression or unacceptable toxicity arises, as seen with ibrutinib [14, 15]. Our data revealed a notable difference in median treatment durations: 122 days for chemo, 176 days for chemoimmunotherapy, and 373 days for targeted therapy. These durations align with the standard recommended treatment routines. Specifically, ibrutinib showed a median treatment duration of 630 days, and V+O exhibited 308 days, indicative of their respective treatment schedules. The extended duration of ibrutinib therapy suggests its effectiveness.

Improved survival for CLL patients over time, presumably due to improvements in treatment options, has previously been reported based on Swedish [9] and German registry data [10]. This study reinforces these findings, as time-to-event analyses indicate improved OS for patients initiating 1L treatment from 2016 onward, compared to those who began treatment earlier. Huang et al. also observed improved OS post-ibrutinib approval, with a notable survival increase from patients being treated before 2014 to patients being treated in 2014 and onwards [18]. These trends likely stem from ibrutinib's superior progression-free survival compared to chemoimmunotherapy [12], a benefit amplified by the rapid shift to newer therapies after 2016, as shown in our analysis.

In conclusion, the rapid integration of targeted therapies, such as ibrutinib and venetoclax, following their approval and inclusion in oncologist guidelines, has significantly reshaped the treatment landscape for CLL among SHI-insured individuals in Germany. Over time, these therapies gradually replaced chemoimmunotherapy-based approaches, solidifying their position as standard-of-care options. The observed favourable OS outcome in patients commencing treatment during the widespread adoption of ibrutinib-based therapies underscores the marked improvement in CLL management attributed to these targeted treatments. Furthermore, our findings not only emphasize the clinical benefits associated with the adoption of targeted therapies but also highlight the rigorous adherence to established guidelines within the German healthcare framework. This steadfast adherence not only ensures the consistent implementation of evidence-based practices but also reflects the adaptability of the healthcare system in accommodating and optimizing CLL treatment strategies amidst a constantly evolving therapeutic landscape.

4.1 | Limitations

This study, based on claims data representing a selected subpopulation, may have limited generalizability to the broader German population. Potential biases such as variations in demographic composition, may impact patient fitness and consequently, the treatment regimens received. The therapy detection algorithm, using a heuristic approach, cannot distinguish between combination therapies and immediate switches of substances due to intolerance. To address this issue, prescriptions occurring only once per patient were excluded to mitigate this effect. Additionally, our definition of an incident patient (four quarters insured without a CLL diagnosis prior to the first diagnosis) is an approximation, and we cannot exclude the possibility that some detected 1L therapies might be RF therapies. The dataset's commencement in 2010 and the requirement for incidence also mean fewer RF therapies initially, leading to increased variability. The dataset lacks clinical details such as progression, staging, biological risk factors (e.g. TP53 mutations, deletion of chromosome 17p and IGHV status) or outcome data. This limitation restricts our ability to differentiate between CLL subtypes, analyse their specific treatment patterns, and conduct a comprehensive time-to-event analysis.

AUTHOR CONTRIBUTIONS

Hannes Wartmann and Timm Volmer designed the study. Hannes Wartmann and Anna Kabilka analysed the data. Hannes Wartmann, Timm Volmer and Norbert Schmitz interpreted the results. Hannes Wartmann and Anna Kabilka drafted the manuscript. Timm Volmer and Norbert Schmitz reviewed the manuscript. Barthold Deiters supplied the data and methodical support. All authors participated in revising and finalizing the manuscript and approved it for submission.

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CONFLICT OF INTEREST STATEMENT

Barthold Deiters is employed at the GWQ ServicePlus AG, which was founded and is owned by a group of health insurance companies. Timm Volmer, Hannes Wartmann and Anna Kabilka are employed by SmartStep Data Institute, which works as a scientific partner institute to SmartStep Consulting, a private sector entity specialized in market access consulting. Furthermore, the authors declare that they have no competing interests.

FUNDING INFORMATION

No direct funding has been recieved for this research.

DATA AVAILABILITY STATEMENT

Because of the confidential nature of in- and outpatient claims data, permission for public availability of the data is not possible. The permission to access the data is restricted to research and subjects to the consent of the health insurance funds.

ETHICS STATEMENT

Ethical approval was not required, as German law allows for analysing anonymous data for research purposes without patients' consent.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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