

Improved Survival of Patients With Chronic Lymphocytic Leukemia Between 1998-2022, Including the Era of Target Therapies With BCL2 and BTK Inhibitors

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Abstract. *Background/Aim: The treatment for chronic lymphocytic leukemia (CLL) has changed dramatically over the last two decades. The current study aimed to investigate the impact on overall survival (OS) and time to next treatment (TTT) among CLL patients from 1998 to 2022. Patients and Methods: The cohort was based on data obtained from electronic medical records of Maccabi, the second largest healthcare organization in Israel. All included patients were diagnosed with CLL based on the IWCLL criteria and complete clinical, laboratory, and treatment data were available. The study encompassed 3,964 patients diagnosed with CLL during the specified study period. Results: Patients with CLL who required therapy were divided into three eras based on the dominant treatment approach: chemotherapy alone before 2010, therapy with chemotherapy and anti-CD20 between 2010 and 2017, and therapy with targeted agents between 2017 and 2022. Median OS was 4.1 years, 7.5 years, and not reached, respectively. The six-year OS rates were 40%, 55%, and 69%, respectively, ($p=0.0001$). The median time to the next treatment improved from 5.5 years before 2010, to 8.3 between 2010-2017, to not reached after 2017 ($p=0.0021$). Conclusion: Marked improvements in survival subsequent to fundamental changes in first-line therapy were found in patients with CLL from before 2010 to after 2017.*

Chronic lymphocytic leukemia (CLL) represents the most frequent leukemia in the western world with an incidence of

4-6/100,000 inhabitants per year. Based on the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines, only symptomatic patients, with advance stage are recommended to receive therapy (1). These recommendations are based on several phase III studies, which have evaluated the role of treatment in early-stage disease (2-5). None of the studies demonstrated an improvement in overall survival (OS), and the wait and watch policy remains the gold standard for asymptomatic CLL patients.

For symptomatic patients with advanced stage who require therapy, treatment has changed dramatically over the last two decades. Initially, chemotherapy alone using chlorambucil as the backbone drug was common. This was followed by purine analog-based regimens using fludarabine as monotherapy (6), and then regimens combining fludarabine with cyclophosphamide (FC regimen) (7). Subsequently, the era of chemo-immunotherapy emerged, combining chemotherapy with anti-CD20 antibodies, leading to regimens such as FC+rituximab (FCR) (8, 9) or bendamustine+rituximab (BR) (10).

Historically, the use of the FCR regimen was the first combination to demonstrate an improvement in OS in patients with CLL who receive therapy (9). Following its publication in 2010, it has become the gold standard therapy for FIT CLL patients (8, 9).

Another two regimens, which contain anti-CD20 antibodies and a single chemotherapy drug, have become effective combinations for less fit patients based on results of the CLL10 study, which combined bendamustine with rituximab (10) or the CLL11 study, which was based on the use of chlorambucil with the new generation anti-CD20 antibody, obinutuzumab. These studies demonstrated superiority in terms of progression-free survival (PFS) and OS in comparison to the combinations of chlorambucil with the veteran anti-CD20, rituximab (11).

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Table I. Demographic clinical and treatments parameters of the whole cohort.

Variable	Diagnosis period			p-Value
	Pre-2010 (N=1,626)	2010-2017 (N=1,068)	2017-2022 (N=1,270)	
Age	66.4 (57.8-74.7)	67.8 (59.8-76.5)	69.4 (60.3-76.2)	0.351
<65	623 (38.3%)	392 (36.7%)	454 (35.7%)	
≥65	1,003 (61.7%)	676 (63.3%)	816 (64.3%)	
Sex				0.943
Female	685 (42.1%)	457 (42.8%)	539 (42.4%)	
Male	941 (57.9%)	611 (57.2%)	731 (57.6%)	
BINET				0.594
A or B	1,580 (97.2%)	1,041 (97.5%)	1,229 (96.8%)	
C	46 (2.8%)	27 (2.5%)	41 (3.2%)	
Follow-up-time (in months)	158 (76-204)	79 (75-120)	27 (13-46)	<0.001
Smoking status				<0.001
Unknown	108	13	24	
No	1,219 (80.3%)	802 (76.0%)	915 (73.4%)	
Quit	135 (8.9%)	118 (11.2%)	140 (11.2%)	
Yes	164 (10.8%)	135 (12.8%)	191 (15.3%)	
Treatment status				<0.001
T-Naïve	1,153 (70.9%)	693 (64.9%)	994 (78.3%)	
Treated	473 (29.1%)	375 (35.1%)	276 (21.7%)	
Treated by Anti-CD20				<0.001
No	125 (7.7%)	82 (7.7%)	128 (10.1%)	
Yes	348 (21.4%)	293 (27.4%)	148 (11.7%)	
Treated by novel agent				<0.001
No	180 (11.1%)	69 (6.5%)	14 (1.1%)	
Yes	293 (18.0%)	306 (28.7%)	262 (20.6%)	
No. treatment lines				<0.001
1	251 (15.4%)	187 (17.5%)	197 (15.5%)	
2	115 (7.1%)	130 (12.2%)	52 (4.1%)	
>2	36 (2.2%)	25 (2.3%)	3 (0.2%)	

The novel era of targeted therapy has emerged in the last decade with three novel drug families: the BTK inhibitors (BTKIs), BCL2 inhibitors (BCL2Is), and PI3K inhibitors (PI3KIs).

These drugs demonstrated high response rate in relapse refractory CLL and treatment naïve patients. Indeed, several phase III clinical trials that compared chemo-immunotherapy to targeted therapy have reported improved PFS both in standard-risk patients as well as in high-risk patients, such as those harboring *TP53* mutations or 17P deletion. First was the use of ibrutinib, first generation BTKI with and without anti-CD20 antibody (12, 13), followed by 2nd generation BTKIs such as acalabrutinib (14) and zanibrutinib (15, 16). The BCL2I venetoclax has introduced a new concept into the field of targeted therapies. It is administered as a time-limited drug for 12-24 months, often combined with obinutuzumab or rituximab (17, 18). Based on the above, the use of BTKIs, BCL2Is, and anti-CD20 have become the standard of care for patients with CLL (19).

The aim of the current work was to investigate the survival of patients with CLL in different eras of treatment,

with a major interest on the impact of the introduction of targeted therapies in a large cohort of patients. Additionally, we aimed to evaluate how the changes in administered treatment have impacted the OS of patients with CLL.

Patients and Methods

The cohort is based on data obtained from electronic medical records, after receiving approval from the ethical committee of the Maccabi healthcare organization, the second-largest in Israel, with approximately 2.5 million insured patients. The study period begins on January 1st, 1998 and ends on December 31st, 2022.

We analyzed the outcome of all patients with CLL, diagnosed based on the IWCLL diagnostic criteria, for whom complete clinical, laboratory and therapy data were available (Table I). Univariate analysis was conducted on all variables to assess their association with the diagnosis period. Continuous variables like age were analyzed using Mann–Whitney *U*-test. Categorical variables like sex were analyzed using Chi-square test. Variables with *p*-value <0.05 are

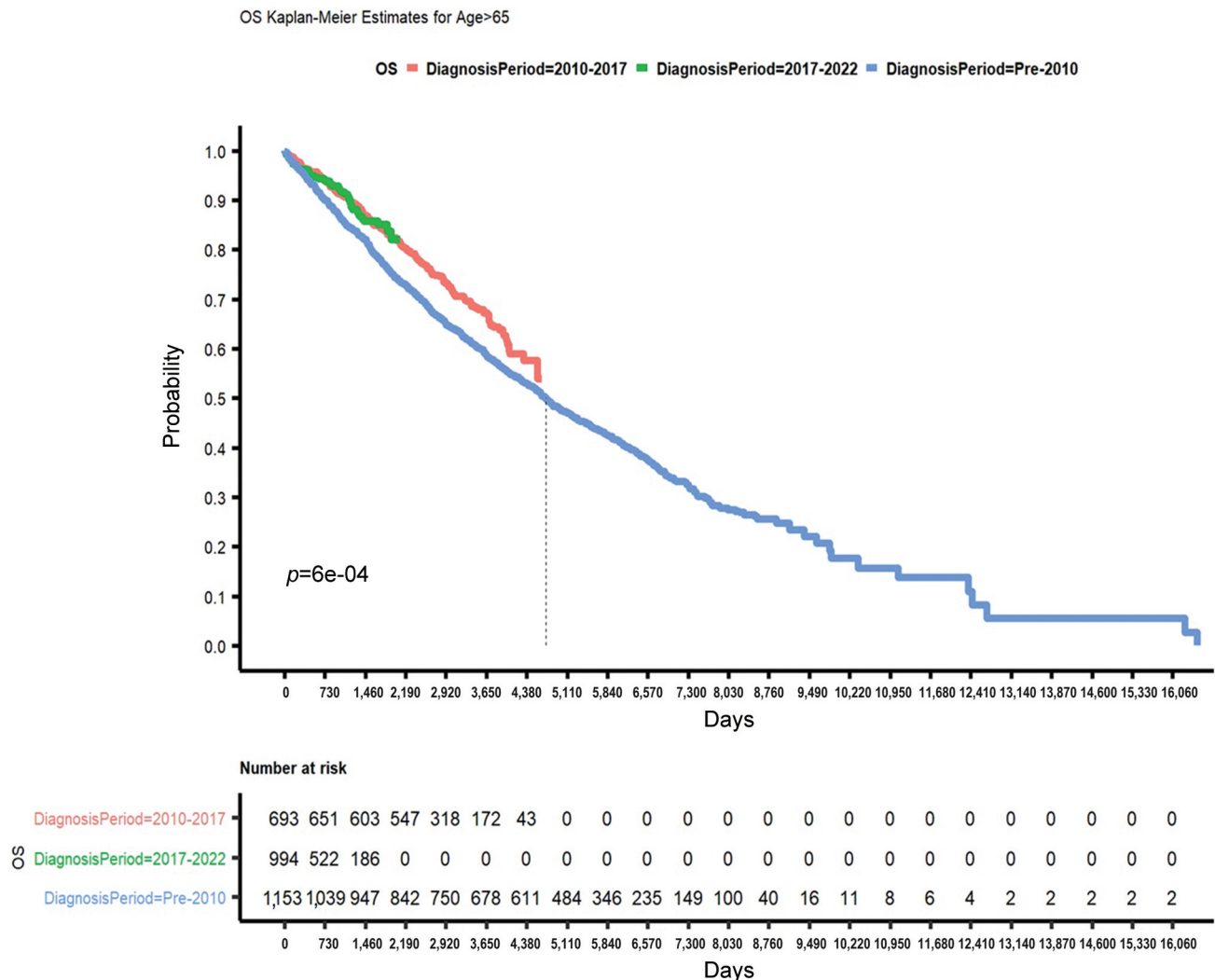


Figure 1. Overall survival of patients with chronic lymphocytic leukemia (CLL) in "wait and watch", during the last 24 years, divided into three treatment eras: before 2010, between 2010 and 2017 and between 2017 and 2022.

considered statistically significant. Survival curves for OS and time to treatment were estimated using the Kaplan-Meier method and compared using a two-sided log-rank test. All statistical analyses were performed using the R statistical software 4.3.1 (2023-06-23) (Foundation for Statistical Computing, Vienna, Austria).

Results and Discussion

During the study period, 3,831 patients with CLL based on the IWCLL criteria were included. Median age at diagnosis of the entire cohort was 67.8 years (range=59-75.7 years). Males represent 57.6% of our cohort, median age at therapy administration was 70.6 years (range=62-76.8 years), and median duration from diagnosis to treatment was 54 months

(range=17-107 months). A total of 2,840 patients had never received therapy; 1,153 patients before 2010, 693 patients who were diagnosed between 2010 and 2017, and 994 patients who were diagnosed between 2017 and 2022. Median OS of the entire cohort was 13.1 years. Five years OS was 81%. No significant change in survival was observed in patients who were on active surveillance (Figure 1).

Patients with CLL who required therapy were divided into 3 eras based on the available therapy at that era: Chemotherapy alone before 2010 (213 patients), therapy with chemotherapy and anti-CD20 antibody between 2010 and 2017 (380 patients), and targeted therapies between 2017 and 2022 (531 patients). Median OS was 4.1 years, 7.5 years and not reached for treatment periods pre-2010, between 2010 and 2017 and between 2017 and 2022 respectively,

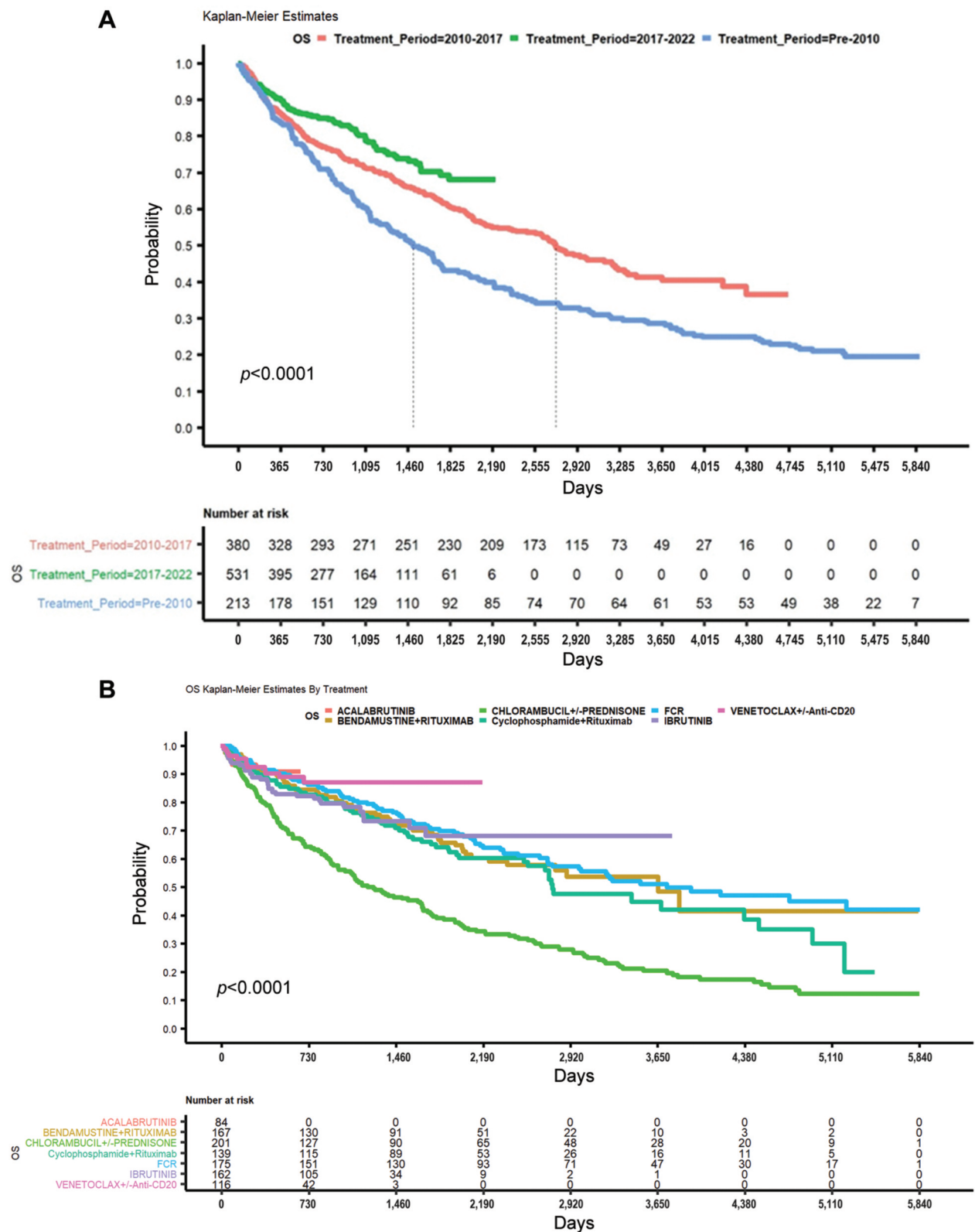


Figure 2. Overall survival of treated patients with chronic lymphocytic leukemia (CLL) during the last 24 years. A) Overall survival divided into three treatment periods: before 2010, between 2010 and 2017, and between 2017 and 2022. B) Overall survival of patients with CLL during the last 24 years according to treatment.

whereas 6 years OS was 40%, 55%, and 68%, for treatment periods pre-2010, between 2010 and 2017 and between 2017 and 2022 respectively, with a p -value of 0.0001, indicating significant improvement in survival (Figure 2A).

For evaluation of OS for each treatment regimen separately, we included only treatment that was given to at least 50 patients; 6 years OS based on therapy given was not reached for acalabrutinib treatment, 85% for venetoclax, 68% for Ibrutinib, 65% for FCR, and 60% for BR or chlorambucil+ anti-CD20 antibody therapy in comparison to 35% for patients treated with chlorambucil±prednisone. These results must be interpreted with caution as median follow up for Acalabrutinib was only 12 months (Figure 2B). The median follow up for FCR, ibrutinib, and venetoclax was 79, 29, and 22 months, respectively.

Median time to next treatment after 1st line therapy was improved from 5.5 years before 2010, to 8.3 between 2010 and 2017 to not reached between 2017 and 2022 ($p=0.0021$). Median OS after 1st line of treatment was 4.2 years, 7.6 years and not reached for treatment periods pre-2010, between 2010 and 2017 and between 2017 and 2022, respectively (p -value <0.0001).

Several studies have studied the impact of treatment on the survival of patients diagnosed with CLL in the last decade (20-26). One of the largest studies was performed on the Danish population, which included 10,455 patients with CLL, who were diagnosed between 1978 and 2013 (20). They reported a reduction in the relative risk of death in patients with CLL when the era before 1984 was compared to the era between 2006-2013.

A study from the British Columbia has reported an improved survival outcome with the addition of Rituximab to initial therapy for CLL. They included 1,345 patients who were treated between 1973 to 2014, and median OS was improved from 6.2 years to 8.9 years. Their report is line with our analysis for the era of chemotherapy alone in comparison to the chemo-immunotherapy era (21). Similar outcome was reported by Weide *et al*. (22).

Most of the studies that evaluated the survival of patients with CLL, have not evaluated the impact on survival when comparing the role of BTKIs and venetoclax-based therapy, despite these regimens being the most commonly used currently. One study that evaluated the impact of the introduction of this targeted therapy was based on the US SEER database (27). However, they performed a meta-analysis of published data and did not analyze real world data as in our study.

Interestingly, we observed no improvement in survival in the wait and watch cohort; indicating that the use of supportive care has not changed significantly during the last 25 years. Our results are in line with the Danish study, which reported no change in the risk of death from infections in their large cohort of CLL patients (20).

Study limitations. First, its retrospective nature needs to be considered when comparing indirectly different regimens. Second, an unexpectedly large cohort of patients was included in the wait and watch category. One explanation might be the fact that we have missed some of the patients who were treated with chemotherapy only, as at that era, drugs were not reimbursed or transferred from Maccabi HMO to the medical center who provided the therapy in day care. Yet, patients who were included in the treatment analysis represent an independent large cohort with full available data on therapy and outcome, with significant improvement in survival as reported above. Third, we are missing data regarding immunoglobulin heavy chain variable region genes (IGHV) mutational status and fluorescence in situ hybridization (FISH) results for the majority of patients in our cohort, and therefore these parameters were not included in the analysis. Lastly, our study did not aim to compare the outcome of patients with CLL to the general population, and data regarding healthy controls are not included.

Conclusion

We found marked improvements in relative survival at the population level subsequently to fundamental changes in the first-line therapy of patients diagnosed with CLL. These results are encouraging; the introduction of chemo-free regimens impacts positively on the survival of patients with CLL.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

TT designed, organized, and wrote the manuscript. HA prepared the data and preprocessed the data, LR performed the statistical analysis and wrote the manuscript. GM, SG and TP, designed and wrote the manuscript.

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