Retrospective cohort study of real-world treatment patterns and overall survival in patients with chronic lymphocytic leukemia (CLL) diagnosed between 2010-2017 in Ontario, Canada

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Introduction

- Chronic lymphocytic leukemia (CLL) is the most common type of adult leukemia in Canada, accounting for about 44% of all leukemias.(1)
- In 2016/17, approximately 1,745 Canadians were diagnosed with CLL, and 611 Canadians died from the disease.(2) CLL affects mainly older patients, with a median age at diagnosis of 71 years (1) and the five-year net survival rate is 83%.(3)
- The majority of CLL patients (>80%) are diagnosed in early stages, and therefore, have long-term indolent disease not requiring treatment until onset of symptoms.(4, 5)
- Current recommendations for first line (1L) treatment for fit, younger CLL patients without high-risk cytogenetics, is a combination of fludarabine, cyclophosphamide and rituximab (FCR). (6) For older, unfit patients, 1L chlorambucil (Chlo) in combination with obinutuzumab (C+O) is often used.
- Newer targeted therapies (e.g., ibrutinib) have proven effective in those considered FCR-ineligible, and have improved efficacy compared to C or C+O.(6,7)

Objective

- There is limited data outside of clinical trials on real-world outcomes for Canadian CLL patients treated with new agents. Consequently, the objective of this study was to report on the treatment patterns and outcomes associated with CLL using population-level administrative datasets in Ontario, Canada.

Methods

- DESIGN: Longitudinal, population-level study of CLL patients diagnosed between January 1, 2010 and December 31, 2017 from the Ontario Cancer Registry (OCR), with follow-up until December 2018.
- ETHICS: This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre.
- DATA SOURCES: Administrative data from the OCR and 11 other health databases.
- PATIENT POPULATION: Patients had to be at least 18 years of age with valid provincial coverage, diagnosed with CLL based on the ICD-O-3 histology code 9823/3- CLL or small cell leukemia, and survived more than 2 weeks after diagnosis. Patients were included if any of the following treatment were administered regardless of line of therapy: bendamustine (bend), bendamustine+rituximab (BR), chlo, C+O, cyclophosphamide (cyclo), FCR, ibrutinib, idelalisib+rituximab, rituximab, and venetoclax. Baseline characteristics for treated patients were included.

Results

- 2,887 CLL-treated patients were identified, and Table 1 baseline characteristics shows a median age of 68 years and 67% male distribution. Patients were stratified by treatment, irrespective of line of therapy (Table 1).
- FCR was the therapy most often used in the overall cohort (35%). Use of FCR steadily decreased over the time period studied, with C+O or ibrutinib being more frequently used in 2017 or 2018, and more frequently used in older patients.
- FCR-treated patients also had less comorbidities at diagnosis compared to patients who received C+O or ibrutinib; 13% had chronic obstructive pulmonary disease (COPD) vs. 20.2% for C+O or 18.5% for ibrutinib; 18.6% of FCR-treated had diabetes compared to 30.4% for C+O or 25.6% for ibrutinib. 9.5% of FCR-treated patients had prior cancer compared to 19.5% for C+O or 18.8% for ibrutinib.

Table 1. Demographic table of CLL diagnosed patients in Ontario between January 2010 to December 2017 stratified by the treatment.

	C+O	FCR-based	Ibrutinib	Other*	Total
	N=421	N=1,009	N=352	N=1,105	N=2,887
CLL diagnosis year					
2010	28 (6.7%)	119 (11.8%)	10 (2.8%)	185 (16.7%)	342 (11.8%)
2011	27 (6.4%)	137 (13.6%)	22 (6.3%)	172 (15.6%)	358 (12.4%)
2012	32 (7.6%)	145 (14.4%)	17 (4.8%)	145 (13.1%)	339 (11.7%)
2013	45 (10.7%)	151 (15.0%)	22 (6.3%)	170 (15.4%)	388 (13.4%)
2014	54 (12.8%)	148 (14.7%)	39 (11.1%)	125 (11.3%)	366 (12.7%)
2015	91 (21.6%)	125 (12.4%)	68 (19.3%)	120 (10.9%)	404 (14.0%)
2016	72 (17.1%)	89 (8.8%)	76 (21.6%)	101 (9.1%)	338 (11.7%)
2017	72 (17.1%)	95 (9.4%)	98 (27.8%)	87 (7.9%)	352 (12.2%)
Age at index					
Mean ± SD	73.55 ± 6.84	61.09 ± 9.39	67.92 ± 10.67	73.09 ± 10.82	68.33 ± 11.28
Median (IQR)	74 (69-78)	61 (55-67)	69 (62-76)	74 (66-82)	69 (61-77)
Age at treatment					
Mean ± SD	76.09 ± 6.38	62.63 ± 9.17	70.60 ± 10.33	74.47 ± 10.77	70.10 ± 11.17
Median (IQR)	76 (72-81)	63 (56-69)	71 (65-77)	76 (67-83)	71 (63-78)
Sex					
Female	131 (31.1%)	299 (29.6%)	105 (29.8%)	430 (38.9%)	965 (33.4%)
Male	290 (68.9%)	710 (70.4%)	247 (70.2%)	675 (61.1%)	1,922 (66.6%)
Charlson Comorbidity index					
Mean ± SD	1.06 ± 1.65	1.30 ± 1.59	0.95 ± 1.47	1.92 ± 2.03	1.46 ± 1.81
Median (IQR)	0 (0-2)	0 (0-2)	0 (0-2)	2 (0-3)	1 (0-2)

* Other treatments/regimens include bendamustine (monotherapy or in combination with rituximab), cyclophosphamide, rituximab monotherapy, chlorambucil monotherapy, idelalisib and venetoclax.
**Exact counts suppressed due to small cell size and for privacy reasons.

1L Treatment Patterns

- The mean time from diagnosis to 1L treatment was 651 days with 35% of patients receiving FCR-based treatment.
- Figure 1 shows the shift in 1L treatment approach over time. Starting in 2015, C+O and ibrutinib utilization increased while FCR and chlorambucil monotherapy decreased. By 2018, 27% of patients received C+O, 27% received ibrutinib and 24% received FCR.

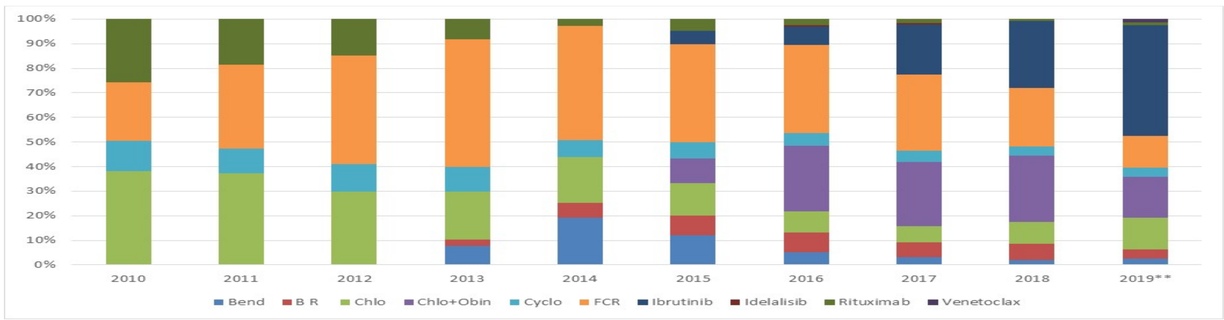

Figure 1: First line treatment regimen received from 2010-2019 (incomplete annual data).**

2L and 3L Treatment Patterns

- The mean time from end of 1L to start of second line (2L) treatment was 1.74 years. Less then a third of 1L-treated CLL patients (N=827) received a 2L treatment, with ibrutinib as the most frequently (65%) 2L-administered treatment. Both 1L FCR-treated (78%) and C+O-treated (89%) patients went on to receive 2L-ibrutinib.
- Of the 17 patients who received 2L-venetoclax, upon progression or treatment switch, patients either received ibrutinib (33%), chlo (33%) or cyclo (33%). In patients who received prior ibrutinib, 41% received venetoclax in third line (3L).
- 124 patients received 3L treatment and mean between treatment time was 0.98 years.

Survival

- Median overall survival (mOS) was stratified by before/after 2015 to capture changes in public reimbursement of agents such as obinutuzumab and ibrutinib in Ontario.
- In Figure 2, mOS was 6.2 years in patients diagnosed and treated before 2015 (left), and mOS was not reached in patients who were diagnosed/initiated treatment after 2015 (right).

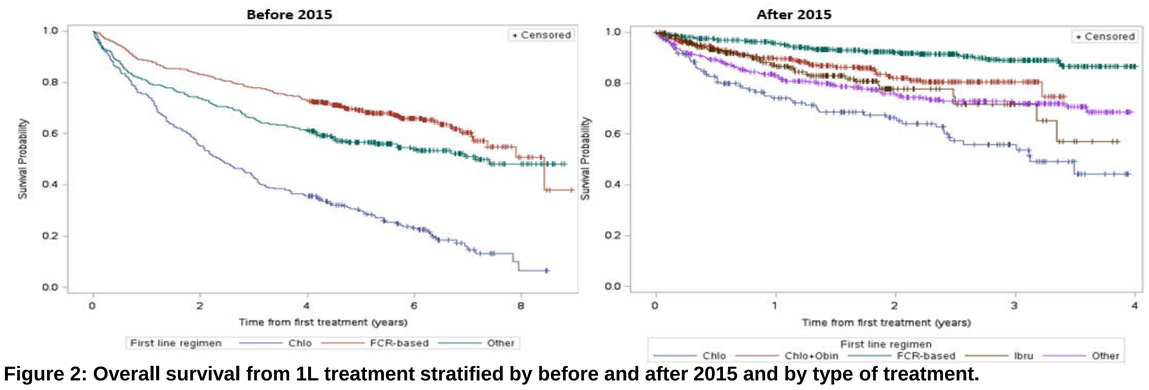

Figure 2: Overall survival from 1L treatment stratified by before and after 2015 and by type of treatment.

- 1- and 5-year survival from 1L treatment initiation was 86% and 61%, respectively.
- 1-, 3- and 5-year survival of 1L FCR-treated patients was 93%, 83% and 74%, respectively; for 1L C+O-treated patients, 1- and 3-year survival was 90% and 81%, respectively.
- In 2L, majority of patients received ibrutinib and survival was longer compared to the “other” group; 87% vs.73% in year 1, and 61% vs. 42% in year 4, respectively.
- For 3L, the same trend was observed with longer survival of ibrutinib-treated patients compared to the “other” group: 75% vs 57% in year 1 and 70% vs. 45% in year 2. mOS was 3.8 versus 1.3 years, respectively.

Conclusions

- A shift in treatment patterns for CLL can be seen with the introduction of newer therapies, such as ibrutinib in 2015.
- Population-level results can support healthcare decision-makers by characterizing the size of CLL patient populations, identifying real-world treatment patterns and calculating survival outcomes.

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