Predicting Optimal Treatment Regimen To Improve Outcomes Of Patients With CLL/SLL Using Random Survival Forest

MSR83

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Background

- Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are similar, slow-growing types of blood cancers that affect the lymphocytes
- Average 5 and 10-year survival rates after initial CLL diagnosis are estimated as 88% and 78%, respectively (SEER, 2023)
- Patient care has evolved with the introduction of targeted therapies such as covalent Bruton tyrosine kinase inhibitor (cBTKi), B-cell lymphoma-2 inhibitor (BCL2i), etc.
- Individualized treatment regimens aim to address the question of identifying the most suitable treatment option for a given patient. However, optimal treatment have not been comprehensively studied in this disease setting
- **Objectives**: To predict optimal treatment regimen classes in first and second lines of therapy (LOT) that maximizes overall survival (OS) in patients with CLL or SLL by using random survival forest (RSF) for clinical decision-making.

Study Design/Methods

- The study used the nationwide, longitudinal Flatiron Health electronic health record-derived, deidentified database, comprising patient-level data originated from ~280 cancer clinics (~800 sites; primarily community oncology settings) and curated via technology-enabled abstraction.
- Eligible patients were adults diagnosed with CLL/SLL who received ≥1 LOT between January 1, 2016 and August 31, 2023.
- Individualized regimens were grouped into hierarchy regimen classes; the five most common were included in this analysis.
- Study cohorts were randomly partitioned 1000 times into 80% training and 20% testing subsets.
- RSF models were used to predict optimal regimen classes in first and second LOT based on baseline demographics and clinical characteristics.
- The OS expected under the predicted optimal treatment regimen was compared to that under the current prescribing practice by using Cox proportional hazards regression, adjusted for baseline characteristics imbalance by inverse probability weighting.

§ Detailed patient and clinical characteristics are available upon request.
* 95% prediction intervals (PI) based on 1000 random split replications.
# Larger importance scores indicated greater relative importance of a variable among all other variables in the RSF model.
Abbreviations: ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; $RMST_{10}$ = restricted mean survival time at 10 years; SES = socioeconomic status

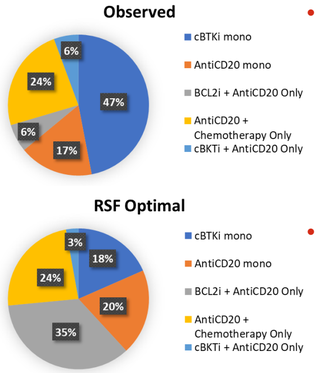
Results

- The study cohort included 7,219 and 2,252 patients with first and second LOTs, respectively.

Table 1. Differences in baseline characteristics among top 5 regimen classes

Baseline Variable §	P-value comparing regimen classes at 1st line start	P-value comparing regimen classes at 2nd line start
Age, year	<.0001	0.0001
Sex (female, male, unknown)	<.0001	0.0009
Race (White, Black/African American, other, unknown)	<.0001	0.1794
Ethnicity (Hispanic/Latino, Not Hispanic/Latino, unknown)	0.0000	0.4608
Practice Region (Northeast, Midwest, South, West)	<.0001	0.0003
SES Index 2015-2019 (1, 2, 3, 4, 5, unknown)	0.0028	0.1037
ECOG performance status (0-1, 2+, unknown)	<.0001	<.0001
Rai Stage (0, I, II, III, IV, not documented)	<.0001	0.0278
Time from Diagnosis to 1st/2nd Line Start, respectively	<.0001	<.0001
Deletion11q (mutated, unmutated, unknown)	<.0001	<.0001
Deletion13q (mutated, unmutated, unknown)	<.0001	<.0001
Deletion17p (mutated, unmutated, unknown)	<.0001	<.0001
Trisomy12 (mutated, unmutated, unknown)	<.0001	<.0001
Disease Subtype (CLL, SLL, CLL/SLL)	<.0001	0.1731
Hepatosplenomegaly (true, false)	<.0001	0.1410
Lymphadenopathy (true, false)	<.0001	0.0038
Practice Type (academic, community)	<.0001	0.0011
AntiCD20 in 1st LOT (yes, no)	N/A	<.0001
BCL2i in 1st LOT (yes, no)	N/A	0.0251
cBTKi in 1st LOT (yes, no)	N/A	<.0001
PI3Ki in 1st LOT (yes, no)	N/A	0.7728
Payer Category	<.0001	0.0036

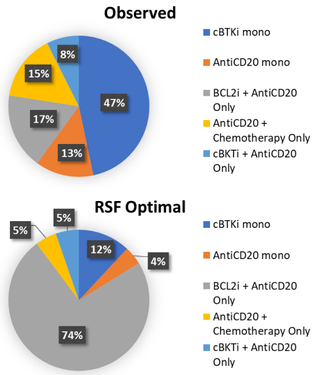
Figure 1. Observed vs RSF optimal treatments in 1st LOT



- Patterns of treatment observed in real-world practice differed from what was predicted to be optimal by RSF models (20.5% "on optimal")
- Mean estimates of $RMST_{10}$ and $\widehat{HR}$ predicted gains in overall survival (year) if patients were to follow predicted optimal treatment assignments

Event	Test N	On %	Observed $RMST_{10}$*	RSF Opt. $RMST_{10}$*	$\widehat{HR}$*
OS	1442	20.5	6.7 (6.6, 6.9)	6.9 (6.2, 7.6)	0.86 (0.67, 1.1)

Figure 2. Observed vs RSF optimal treatments in 2nd LOT



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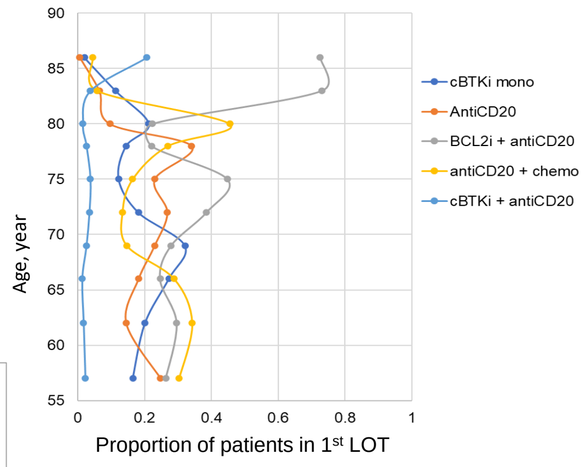
Event	Test N	On %	Observed $RMST_{10}$*	RSF Opt. $RMST_{10}$*	$\widehat{HR}$*
OS	449	20.5	6.1 (5.8, 6.5)	6.7 (4.6, 8.3)	0.76 (0.4, 1.2)

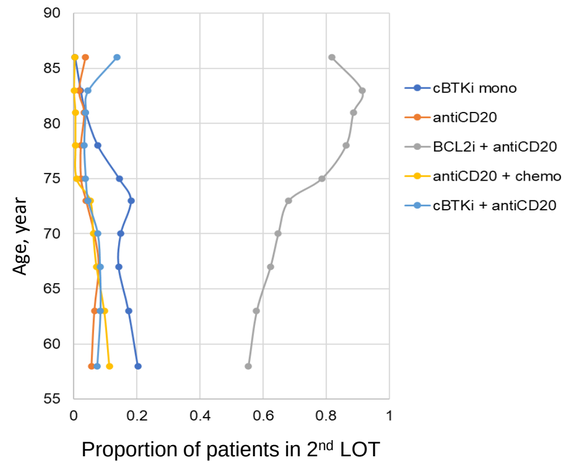
Figure 3. Variable importance in 1st LOT

Variable	Importance score (95% PI) #
Age at Line 1 start	0.44 (0.32, 0.54)
Time from diagnosis to Line 1 start	0.25 (0.20, 0.31)
Rai stage	0.25 (0.20, 0.31)
Payer category	0.24 (0.19, 0.28)
Practice region	0.23 (0.18, 0.28)
SES Index	0.23 (0.17, 0.28)
ECOG performance status	0.22 (0.17, 0.28)
Sex	0.17 (0.12, 0.22)
Lymphadenopathy	0.15 (0.11, 0.20)
Race	0.15 (0.11, 0.19)

Figure 4. Variable importance in 2nd LOT

Variable	Importance score (95% PI) #
Age at Line 2 start	0.23 (0.09, 0.40)
Time from diagnosis to Line 2 start	0.16 (0.06, 0.27)
SES Index	0.15 (0.05, 0.26)
Rai stage	0.13 (0.05, 0.23)
ECOG performance status	0.12 (0.04, 0.22)
Practice region	0.11 (0.03, 0.21)
Payer category	0.10 (0.03, 0.21)
Line 1 contains cBTKi	0.10 (0.03, 0.21)
Sex	0.10 (0.03, 0.21)
Race	0.09 (0.02, 0.19)





Conclusions

- RSF was feasible using oncology EHR data, building the evidence to inform how machine learning may provide recommendations for oncologists in choosing individualized treatments that may be associated with improved outcomes for patients with CLL/SLL.
- In L1 and L2 settings, RSF models predict a different pattern of treatment than currently observed in real-world practice. Future work should focus on evaluating optimal treatment sequencing strategy.
  - In part due to increasingly recommending BCL2i + antiCD20.
  - Limitations: Restricted to treatments observed in real world practice; Only top 5 treatment regimens were considered; Sample size was limited for later lines of therapy; Survival analyses sensitive to censoring rate. The RSF models do not take into account what is known from RCTs and may misinterpret data based on limited variables.

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