HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2020 January 01.

Published in final edited form as:

Cancer. 2019 January 01; 125(1): 135–143. doi:10.1002/cncr.31738.

Real-World Testing and Treatment Patterns in Chronic Lymphocytic Leukemia: A SEER Patterns of Care Analysis

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Abstract

Background: Laboratory testing and treatments have changed dramatically in chronic lymphocytic leukemia (CLL) within the last decade. We evaluated changes in patterns of real-world testing and treatment over time by comparing two population-based cohorts.

Methods: The National Cancer Institute (NCI) sponsored Patterns of Care study was conducted among CLL patients sampled from 14 Surveillance, Epidemiology, and End Results (SEER) program registries. Demographics, testing, and treatment data were abstracted from medical records within 24 months of diagnosis.

Results: 1,008 patients diagnosed in 2008 and 1,367 patients diagnosed in 2014 were included. There was a significant increase in fluorescence *in situ* hybridization (FISH) testing, IgV_H mutation analyses, and lymph node biopsies between 2008 and 2014. FISH testing was performed in the majority of, but not all, treated patients (53% in 2008, increased to 62% in 2014). Some differences in receipt of FISH testing by age and insurance status were observed over time (older patients and Medicare patients without private insurance were less likely to be tested in 2014). There were contrasting testing patterns by practice type and year, with non-teaching hospitals more likely to perform bone marrow biopsies in 2008, and teaching hospitals more likely to perform FISH and IgV_H testing in 2014. There were also differences in treatments over time, with the use of bendamustine and rituximab (BR) being more common in 2014 at the expense of fludarabine, cyclosporine, and rituximab (FCR).

Conclusions: There are been rapidly changing practices of testing and treatment patterns for CLL patients in the last decade.

Precis

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Presented in part at the American Society of Hematology Annual Meeting, Atlanta, GA, December 2017.

All authors have no conflicts of interest to disclose.

Chronic lymphocytic leukemia has advanced in both prognostic testing and therapy over the last decade. Using the National Cancer Institute SEER Patterns of Care dataset from 2008–2010 and 2014–2016, we demonstrate that both testing and treatment patterns have rapidly evolved in a short period of time, and observe some differences in testing by age, insurance status, and type of oncology practice.

Keywords

chronic lymphocytic leukemia; SEER; patterns of care; testing; treatments

INTRODUCTION

The management of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) has undergone substantial changes in the use of both prognostic laboratory testing and standard of care therapy within the last decade. Prognostic testing has included immunoglobulin heavy-chain variable region gene (IgV_H) mutation status,[1] genetic abnormalities identified by FISH,[2] expression of ZAP-70[3] and CD38,[4] and chromosomal karyotyping.[5,6] Of these, IgV_H mutation status and FISH abnormalities have been most thoroughly studied and incorporated into clinical trials. These tests have evolved from purely prognostic information into standard testing needed to personalize therapy. As a result, they have been recommended to be performed in all newly diagnosed CLL patients prior to therapy.[7] In contrast, lymph node biopsies are generally reserved for cases of CLL/SLL that do not present with peripheral blood lymphocytosis adequate for initial diagnosis, while bone marrow biopsies are no longer done routinely but are reserved for particular clinical situations (ex. evaluating cause of cytopenias).[8]

The treatment of CLL has also changed dramatically within a short time span because of the identification of new agents. Bendamustine was approved for frontline therapy in CLL in 2008.[9] Since then, trials comparing bendamustine and rituximab (BR) versus FCR in patients of various ages were performed. A non-inferiority study showed more clinical benefit for patients < 65 years with FCR, with no difference in clinical benefit between FCR and BR among older patients.[10] The Bruton tyrosine kinase inhibitor ibrutinib was approved for relapsed CLL and for frontline therapy in patients with del17p in 2014.[11] It was recently approved for frontline therapy in 2016.[12]

The SEER Patterns of Care study, sponsored by NCI, was conducted in a population of CLL patients within participating SEER registries. We used this large population-based dataset to compare testing and treatment patterns among CLL patients diagnosed in 2008 to those diagnosed in 2014. We reviewed the National Comprehensive Cancer Network (NCCN) recommendations for testing and treatment for those years,[13] and compared differences in patterns by type of practice (teaching versus non-teaching hospitals).

METHODS

Data were obtained from the SEER Patterns of Care (POC) studies. The SEER program collects cancer incidence and mortality data from 18 population-based registries that

represent approximately 30% of the US population.[14] These registries primarily rely on hospital based records for their cancer treatment information, and there are known data gaps in therapies (such as oral chemotherapy and hormone therapy) that are delivered in an outpatient setting. The POC studies were implemented to supplement routinely collected SEER information.[15] Each year the SEER program selects certain cancer sites to abstract additional treatment information from a random sample of cases from 14 SEER registries. CLL cases diagnosed in 2008 and 2014 have been included in POC studies. CLL cases were defined by international classification of disease, oncology (ICD-O) histology code 9823. Additional case inclusion criteria included age 20 or older at diagnosis. Exclusion criteria included a previous history of cancer, synchronous diagnosis with another primary cancer, and cases diagnosed at autopsy.

For both years, the POC abstraction form included information on diagnostic procedures (bone marrow exam and lymph node biopsy), testing (fluorescence in situ hybridization (FISH), chromosomal karyotype, and IgV_H mutation testing), systemic therapies, and comorbid conditions. For both years, the list of systemic therapies included: alemtuzumab, bendamustine, chlorambucil, cladribine, cyclophosphamide, fludarabine, flavopiridol, interferon, lenalidomide, obatoclax, pentostatin, prednisone, rituximab, and vincristine. For cases diagnosed in 2014, ibrutinib, idelalisib, obinutuzumab, and ofatumumab were added to the systemic therapies list. Information on the hospital that administered the most definitive therapy was collected based on the American Hospital Association (AHA) reported characteristics which included bed size, residency training approval, and classification (profit versus non-profit). The abstract form was completed by trained SEER abstractors from patient medical records up to 24 months post-diagnosis. In addition, the treating physician was mailed a form to verify treatment and report any treatments that may have been administered in an outpatient setting.

All analyses were completed with SAS version 9.4 (Cary, NC) and were weighted to account for the sampling design. Patient characteristics evaluated included sex, race/ethnicity, age in 10 year groups, Charlson Comorbidity score, an area-based measure of socioeconomic status developed by Yost *et al* that uses US census block-group data,[16] and insurance status at the time of diagnosis. These characteristics were summarized by observed counts and weighted percentages. Percentages are weighted to accurately reflect the entire SEER population rather than absolute percentages of numbers observed among the sampled study cohort, which require adjusting since minority groups are overrepresented in the abstraction. The study abstractors recorded if each test was “performed”, “not performed”, or “unknown if performed”. For both “not performed” and “unknown if performed”, test results were not documented or available in the medical chart, and therefore these groups were combined in this analysis. Receipt of cytogenetics testing was summarized by observed count and weighted percentages and compared by diagnosis year using the Rao-Scott chi-square test. Weighted logistic regression was used to estimate the odd ratios (OR) and 95 percent confidence intervals (95% CI) for receipt of cytogenetic testing. Predictors evaluated included race/ethnicity, and variables that were significantly different in univariate analysis (sex, age at diagnosis, insurance, and receipt of systemic treatment). Odds ratios were estimated for all patients and stratified by age at diagnosis (<65 versus ≥ 65) to assess differences between Medicare recipients with and without private insurance. The most

common systemic treatment regimens by diagnosis year were summarized using observed count and weighted frequencies among those who received systemic therapy. This was further stratified by age at diagnosis (< 70 versus ≥ 70), Charlson comorbidity score (0 versus ≥ 1), and if the treating hospital had a residency program. Testing and treatment patterns were summarized by whether the treating hospital had a residency program (defined as a teaching hospital, those without residency programs defined as non-teaching hospitals) and diagnosis year, and compared using the Rao-Scott chi-square test.

RESULTS

Baseline Characteristics

This study included 1,008 CLL patients diagnosed in 2008 and 1,367 CLL patients diagnosed in 2014. Demographics are depicted in Table 1; age, gender, race, socioeconomic status (SES), Charlson comorbidity index, and insurance status did not differ between the two cohorts. Racial distributions reflect the SEER 14 population and historical trends, with non-Hispanic whites representing the majority of patients.[17]

Trends in CLL Testing

Testing patterns are shown in Table 2. CLL FISH was performed within 2 years of diagnosis for 44% of all diagnosed patients in 2008, which increased significantly to 51% of all patients in 2014 (p = 0.003). The distribution of FISH abnormalities were not different by age (Supplemental Table 1). Among patients who were treated within 2 years of diagnosis, FISH testing occurred in the majority but not all patients (53.4% of treated patients in 2008, which increased to 61.6% of treated patients in 2014). IgV_H mutation analysis was done infrequently during both time periods, but also increased significantly from 6% in 2008, to 11% in 2014 (p<0.001).

Bone marrow biopsies decreased in frequency from 46% of all patients in 2008, to 39% of patients in 2014 (p=0.002). Lymph node biopsies however, were rarely performed in 2008 (5%) and this increased substantially in 2014 (27%, p<0.001). Chromosomal karyotyping, which is often performed with bone marrow biopsies but which can be done with peripheral blood, showed no difference in frequency of testing in 2008 compared to 2014 (35% in both years).

In a separate analysis, we analyzed factors that determined receipt of CLL FISH among age, gender, race, comorbidity, socioeconomic status, and insurance status (Table 3). Younger age was a predictor for receiving FISH testing in both time periods, but only significant in adjusted models for 2014 (aOR=1.30, 95% CI 0.90 to 1.89 in 2008 and aOR=2.32, 95% CI 1.58 to 3.41 in 2014). In 2008, there was no difference in receipt of testing by insurance status. However in 2014, among patients who are 65 years and older, those with Medicare and no private insurance were significantly less likely to receive testing (aOR=0.54, 95% CI 0.36 to 0.82) compared to those with Medicare and private insurance.

Trends in Use of CLL Frontline Treatments

The majority of CLL patients remained untreated within the first 2 years of diagnosis (74% untreated in 2008, and 71% untreated in 2014). Of those patients who were treated within 2 years of diagnosis, we analyzed which frontline treatments were used in each time period (Table 4). Among patients in 2008, FCR was the most used therapy, followed by rituximab monotherapy, FR, and chlorambucil-based therapy. In 2014, BR was the most popular therapy, followed by rituximab monotherapy, FCR, and ibrutinib. In both time periods, chemoimmunotherapy was preferred over rituximab monotherapy in younger patients, however BR was preferred over FCR in 2014. In both time periods, FCR was not commonly used for older patients, or patients with 1 or more comorbid condition.

There was a limited number of patients to evaluate treatment patterns based on identified FISH abnormalities and IgV_H mutation status. The number of patients separated by FISH abnormalities, IgV_H mutation status, and untreated or treated within 2 years from diagnosis is shown in Supplemental Table 2. Patients with higher risk CLL such as del17p, del11q, and unmutated IgV_H status were more frequently treated in both time periods, with an increase in treatments among patients with del17p in 2014. This is presumably related to the known higher probability of earlier onset of progressive disease in such patients. The majority of del17p patients were treated with FCR in 2008, and with ibrutinib in 2014 (data not shown). Of the patients who received IgV_H mutation status testing prior to treatment, a majority of these patients were IgV_H unmutated, with most receiving FCR in 2008, and BR in 2014 (data not shown).

Differences in Testing and Treatment Patterns by Practice Type

Differences in testing and treatment patterns between teaching and non-teaching hospitals are shown in Table 5. CLL FISH testing was more common in teaching hospitals compared to non-teaching hospitals in 2014, although the frequency of FISH testing significantly increased for all hospitals from 2008 to 2014. IgV_H mutation analyses were done infrequently in both teaching and non-teaching hospitals in 2008; however in 2014 teaching hospitals were more likely to perform IgV_H mutation analyses compared to non-teaching (12.1% teaching hospital versus 8.7% non-teaching, p=0.051). Bone marrow biopsies were done more often in non-teaching hospitals in 2008 (50.3% versus 41.2%, p=0.014), with a similar decrease in biopsies by hospital type by 2014 (25.2% and 28.3%). However, among top first line treatments received for all patients, there was no significant difference between teaching and non-teaching hospitals. Although limited in number, we also evaluated the distribution of novel therapies introduced by 2014 (ibrutinib, idelalisib, and obinutuzumab) and there was no difference in use between teaching and non-teaching hospitals.

DISCUSSION

Both testing and treatment for CLL have evolved over the past decade. The SEER POC dataset allows for a thorough analysis of trends in a population-based sample, which represents the larger US population compared to clinical trial or single insurance claim datasets. It differs from the Connect CLL Registry[18], which is a multisite community based registry consisting only of treated CLL patients, as we are able to describe testing and

treatment patterns within 2 years of diagnosis for all CLL patients, including the majority of patients who are initially observed.

We reviewed the NCCN guidelines for the treatment of CLL from 2008–2010 and 2014 through the present.[13] CLL FISH testing is listed as "informative for prognostic determination" since 2009. However, since 2008, FISH testing is incorporated into treatment algorithms for progressive and symptomatic CLL, and treatment recommendations are separated by those with or without deletion 17p. Treatment recommendations are also further separated by age (< or ≥70 years) since 2008, and further separated by "frail, significant comorbidity" (not able to tolerate purine analogs) since 2009. With these distinct treatment algorithms put in place, it is not surprising that FISH is the most common test performed compared to the other available prognostic testing.

FISH testing increased from 53% of treated patients in 2008 to 62% of treated patients in 2014. These frequencies are similar to those reported in the Connect CLL Registry and suggest that further improvements can be made.[19] The reasons for lack of testing remain unclear, although we identified disparities in the likelihood of testing by insurance type and age, with older patients and those without private insurance less likely to have testing performed over time. This is unfortunate since missing deletion 17p patients could worsen clinical outcome by using less efficacious therapies, and treating older patients with deletion 17p is now possible given less toxic options such as ibrutinib. We also observed that FISH testing was more common in teaching hospitals compared to non-teaching hospitals and therefore differences in practice may be contributing. Because of the striking improvement in clinical outcomes among patients with del17p using ibrutinib and venetoclax, we expect that CLL FISH testing will continue to increase in the future.[20, 21]

In contrast, IgV_H mutation analyses has remained prognostic and not incorporated into guideline treatment algorithms since 2009. Now that FCR has also demonstrated a greater than 10-year progression free survival in a sizeable fraction of patients with mutated IgV_H status,[22, 23] there may be an increase in the use of this test in the future. Newer prognostic models such as the CLL International Prognostic Index[24] also incorporate IgV_H mutation analyses, as well as *TP53* mutation testing, which have become more readily available recently.

Since 2009, guidelines state that flow cytometry of the blood is adequate for diagnosis, while bone marrow biopsies are useful "under certain circumstances" since 2008. We observed that bone marrow biopsies were more commonly practiced in non-teaching hospitals compared to teaching hospitals in 2008, but have decreased in both hospital settings in 2014. However, the significant difference between the hospital settings might again reflect inconsistencies between practice types. In contrast, lymph node biopsies were rarely performed in 2008 and increased significantly in both hospital settings in 2014. It is unclear why the use of lymph node biopsies has increased. There were more patients with deletion 11q in the 2014 cohort (Supplemental Table 2), and these patients often present with bulky lymphadenopathy. It is also possible that there were more cases of small lymphocytic lymphoma in the latter cohort, and coding does not separate CLL from SLL. Additionally, it is conceivable that more biopsies were performed to rule out Richter's

transformation. PET scanning was recognized as a helpful tool to identify areas to biopsy that were concerning for transformation in 2014.[25]

The overall differences in testing patterns between practice types have become more important given the current focus on low-value versus high-value testing. FISH testing would be considered a high-value test since it helps determine appropriate therapy based on a patient's unique characteristics. Under insurance plans that follow value-based insurance design,[26, 27] patient out-of-pocket cost for high-value testing such as CLL FISH should be waived (no cost). The American Society of Hematology Choosing Wisely Campaign provides recommendations to avoid low-value testing, and recommended avoiding baseline and serial CT scans for asymptomatic early stage CLL in 2014.[28] Routine bone marrow biopsies would be considered to be low-value, since they infrequently change management, and are invasive for patients. Well designed value-based clinical pathways might improve the proper use of selected pre-treatment evaluations with predictive usefulness in both teaching and non-teaching hospital settings, and may distribute standard-of-care guidelines more consistently across practice types.[29]

The differences in treatment regimens used during both time periods are consistent with the NCCN guideline algorithms for age and performance status/comorbidities. It is notable that FCR was not commonly used for patients > 70 years or patients with 1 or more comorbidities during both time periods. BR was more frequently used at the expense of FCR in 2014 among all patients. These trends of the top four frontline treatments received do not necessarily reflect the preferred treatments as listed in the NCCN guidelines by efficacy, but more accurately reflect preferences determined by a combination of age, comorbidities, and toxicity profiles. With the introduction of potent oral therapies such as ibrutinib and venetoclax, the options for patients who are frail and cannot tolerate chemotherapy as well as for patients with high-risk disease have expanded. With these exciting new developments, we expect to see more changes in treatment patterns in the future.

There are several limitations to our study. Only a subset of CLL patients were treated within 2 years of diagnosis which limits the number of patients to analyze treatment patterns. The time of follow up since diagnosis for each cohort was only 2 years, which limits our analysis for time to first treatment and treatment regimens used for more indolent CLL patients. There was only a small subset of non-White patients in our dataset limiting conclusions about any possible effects of racial disparities. Surprisingly, only a minority of patients had 2 or more comorbidities by Charlson Comorbidity Index in our mostly elderly population of CLL patients. We also lack definitive staging (Rai or Binet) with this data set. We are also unable to parse among different indications for rituximab monotherapy, since rituximab may be used as treatment for autoimmune cytopenias rather than systemic CLL therapy. We combined our "not performed" and "unknown" testing groups together, which potentially underestimates the frequency of testing. Despite this, we had similar frequencies of FISH testing as observed in other studies. We are not able to strictly delineate academic centers versus community practices with our dataset and recognize that both academic and community practices have residency programs, but we are still able to observe differences between teaching and non-teaching hospital settings.

Testing and treatment patterns are changing dramatically in the modern era. Testing incorporated into treatment decisions, particularly CLL FISH and IgV_H mutation status, are increasing in frequency from 2008 to 2014. Despite the increase in testing, there remains a significant number of patients who do not undergo FISH and/or IgVH mutation status testing prior to therapy. Some disparities in testing were observed by age and insurance status. FCR was not used commonly among patients who are elderly or have comorbidities. BR is more frequently used compared to FCR in more recent years. There are differences in testing practices when comparing teaching and non-teaching hospitals, with FISH and IgV_H testing performed more frequently in teaching hospitals, and bone marrow biopsies more common in non-teaching hospitals. However, overall trends in CLL therapies used remain similar in teaching and non-teaching hospitals. Given rapid therapeutic developments in CLL, we anticipate dynamic changes in future CLL treatment patterns, and possibly emerging free from standard chemotherapy. Fully evaluating use of these therapies by practice type, and access of these therapies among different patient populations, will be a vital focus of future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This work was supported, in part, by the Epidemiology Research Core (Health and Human Services contract HHS N261201300011I), and NIH Center Grant P30 CA022453 awarded to the Karmanos Cancer Institute at Wayne State University.

REFERENCES

1. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood. 1999;94: 1848–1854. [PubMed: 10477713]
2. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343: 1910–1916. [PubMed: 11136261]
3. Wiestner A, Rosenwald A, Barry TS, et al. ZAP-70 expression identifies a chronic lymphocytic leukemia subtype with unmutated immunoglobulin genes, inferior clinical outcome, and distinct gene expression profile. Blood. 2003;101: 4944–4951. [PubMed: 12595313]
4. Damle RN, Wasil T, Fais F, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood. 1999;94: 1840–1847. [PubMed: 10477712]
5. Thompson PA, O'Brien SM, Wierda WG, et al. Complex karyotype is a stronger predictor than del(17p) for an inferior outcome in relapsed or refractory chronic lymphocytic leukemia patients treated with ibrutinib-based regimens. Cancer. 2015;121: 3612–3621. [PubMed: 26193999]
6. Herling CD, Klaumunzer M, Rocha CK, et al. Complex karyotypes and KRAS and POT1 mutations impact outcome in CLL after chlorambucil-based chemotherapy or chemoimmunotherapy. Blood. 2016;128: 395–404. [PubMed: 27226433]
7. Parikh SA, Strati P, Tsang M, West CP, Shanafelt TD. Should IGHV status and FISH testing be performed in all CLL patients at diagnosis? A systematic review and meta-analysis. Blood. 2016;127: 1752–1760. [PubMed: 26841802]
8. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for diagnosis, indications for treatment, response assessment and supportive management of chronic lymphocytic leukemia. Blood. 2018.

9. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. 2009;27: 4378–4384. [PubMed: 19652068]
10. Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016;17: 928–942. [PubMed: 27216274]
11. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371: 213–223. [PubMed: 24881631]
12. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med. 2015;373: 2425–2437. [PubMed: 26639149]
13. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia Guidelines (Versions 1.2008, 2.2008, 3.2008, 2.2009, 3.2009, 4.2009, 1.2010, 1.2014, 2.2014, 3.2014, 4.2014, 5.2014, 1.2015, 2.2015, 1.2016, 2.2016, 3.2016, 1.2017) Available from URL: www.nccn.org.
14. Howlader N NA, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, and Cronin KA. National Cancer Institute. . SEER Cancer Statistic Review 1975–2014. Available from URL: https://seer.cancer.gov/csr/1975_2014/ 2017].
15. National Cancer Institute: Division of Cancer Control and Population Sciences. Patterns of Care/ Quality of Care Studies. Available from URL: https://healthcaredelivery.cancer.gov/poc/ [accessed March 1, 2018, 2018].
16. Yost K, Perkins C, Cohen R, Morris C, Wright W. Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. Cancer Causes Control. 2001;12: 703–711. [PubMed: 11562110]
17. Li Y, Wang Y, Wang Z, Yi D, Ma S. Racial differences in three major NHL subtypes: descriptive epidemiology. Cancer Epidemiol. 2015;39: 8–13. [PubMed: 25560974]
18. Mato A, Nabhan C, Kay NE, et al. Real-world clinical experience in the Connect((R)) chronic lymphocytic leukaemia registry: a prospective cohort study of 1494 patients across 199 US centres. Br J Haematol. 2016;175: 892–903. [PubMed: 27861736]
19. Mato A, Nabhan C, Kay NE, et al. Prognostic Testing Patterns and Outcomes of Chronic Lymphocytic Leukemia Patients Stratified by Fluorescence In Situ Hybridization/Cytogenetics: A Real-world Clinical Experience in the Connect CLL Registry. Clin Lymphoma Myeloma Leuk. 2018;18: 114–124 e112. [PubMed: 29352719]
20. O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol. 2016;17: 1409–1418. [PubMed: 27637985]
21. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial. J Clin Oncol. 2018;36: 1973–1980. [PubMed: 29715056]
22. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood. 2016;127: 208–215. [PubMed: 26486789]
23. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. Blood. 2016;127: 303–309. [PubMed: 26492934]
24. International CLLIPIwg. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. Lancet Oncol. 2016;17: 779–790. [PubMed: 27185642]
25. Falchi L, Keating MJ, Marom EM, et al. Correlation between FDG/PET, histology, characteristics, and survival in 332 patients with chronic lymphoid leukemia. Blood. 2014;123: 2783–2790. [PubMed: 24615780]
26. de Souza JA, Polite BN, Manning WG, Fendrick AM, Ratain MJ. Value-based insurance design in oncology. Lancet Oncol. 2011;12: 321–323. [PubMed: 21463832]

27. de Souza JA, Ratain MJ, Fendrick AM. Value-based insurance design: aligning incentives, benefits, and evidence in oncology. J Natl Compr Canc Netw. 2012;10: 18–23. [PubMed: 22223866]

28. Choosing Wisely: An initiative of the ABIM Foundation. Available from URL: http://www.choosingwisely.org/clinician-lists/american-society-hematology-baseline-or-routine-surveillance-ct-scans-for-asymptomatic-early-stage-chronic-lymphocytic-leukemia/ [accessed July 2018.

29. Brooks GA, Bosserman LD, Mambetsariev I, Salgia R. Value-Based Medicine and Integration of Tumor Biology. Am Soc Clin Oncol Educ Book. 2017;37: 833–840. [PubMed: 28561700]

Table 1.

Patient characteristics for chronic lymphocytic leukemia (CLL) cases diagnosed in 2008 and 2014 included in the Patterns of Care (POC) studies

	2008	2014
	N (%*)	N (%*)
Total	1,008	1,367
Sex		
Male	535 (59.7)	708 (52.1)
Female	473 (40.3)	659 (47.9)
Study Race		
NHW	802 (85.9)	985 (83.7)
NHB	92 (5.7)	174 (7.1)
Hispanic	79 (5.9)	136 (6.1)
Asian	35 (2.5)	72 (3.2)
Age at Diagnosis		
40–59	214 (22.0)	369 (24.2)
60–69	273 (27.4)	406 (31.9)
70–79	277 (27.2)	340 (25.1)
80+	244 (23.4)	252 (18.7)
weighted mean (SE)	69.6 (0.42)	68.0 (0.05)
Charlson Comorbidity Score		
0	697 (69.5)	935 (70.0)
1	232 (22.8)	340 (23.5)
2	63 (6.2)	69 (5.1)
3 or more	16 (1.5)	23 (1.3)
Yost quintile **		
Group 1 (lowest SES)	125 (11.6)	189 (12.0)
Group 2	174 (17.2)	248 (18.2)
Group 3	191 (19.6)	268 (22.3)
Group 4	236 (24.9)	288 (22.3)
Group 5 (highest SES)	265 (26.8)	343 (25.2)
Missing	17	31
Insurance		
Medicare and Private	357 (35.7)	382 (28.3)
Medicare only	154 (14.4)	292 (22.5)
Private only	331 (35.9)	512 (38.1)
Medicaid or None	119 (10.0)	154 (9.1)
Other or Unknown	47 (4.0)	27 (2.1)

* Percentages are weighted by sampling fraction to reflect the SEER 14 population from which the data were obtained

** The Yost quintile is an area-based measure of socioeconomic status (SES) derived from a principal components analysis of US census block-level data that includes education, household income, 200% poverty level, house value, rent, percent employed, and percent with blue-collar employment.[17]

Table 2.

Receipt of testing and test outcomes for CLL cases diagnosed in 2008 and 2014

	2008	2014	
	N (%*)	N (%*)	p value
Total	1,008	1,367	
FISH performed			0.003
Performed	434 (43.8)	741 (50.7)	
Not Performed / Unknown	574 (56.2)	626 (49.3)	
Karyotype performed			0.841
Performed	337 (34.8)	499 (35.2)	
Not Performed / Unknown	671 (65.2)	868 (64.8)	
Deletions/Trisomy**			<.001
17p deletion	49 (11.6)	50 (6.7)	
11q deletion	16 (4.5)	72 (10.5)	
12 trisomy	38 (11.4)	157 (23.0)	
13q deletion	83 (27.7)	191 (27.0)	
No known deletions/trisomy	158 (44.8)	211 (32.8)	
Unknown	664	686	
Mutated variable immunoglobulin heavy chain			<.001
Performed	63 (6.1)	168 (10.5)	
Not Performed / Unknown	945 (93.9)	1,199 (89.5)	
Bone Marrow Biopsies			0.002
Performed	465 (46.1)	536 (39.0)	
Not Performed / Unknown	543 (53.9)	831 (61.0)	
Lymph Node Biopsies			<.001
Performed	52 (4.9)	385 (26.9)	
Not Performed / Unknown	956 (95.1)	982 (73.1)	

* Percentages are weighted by sampling fraction to reflect the SEER 14 population from which the data was obtained.

** Deletions/trisomy coded hierarchically (in the order listed); i.e. some of the patients with 17p deletions also had other abnormalities. The weighted percentage is among those with FISH testing performed.

Abbreviations: FISH, fluorescent in situ hybridization; CLL, chronic lymphocytic leukemia

Table 3.

Weighted logistic regression results for receipt of FISH testing by diagnosis year

	2008			2014		
	N	**uOR**	**aOR***	**N**	**uOR**	**aOR***
Sex						
Male	535	1.35 (1.03 to 1.78)	1.31 (0.99 to 1.73)	708	1.28 (0.97 to 1.69)	1.10 (0.83 to 1.47)
Female	473	ref	ref	659	ref	ref
Study Race						
NHW	802	ref	ref	985	ref	ref
NHB	92	1.02 (0.64 to 1.61)	1.00 (0.62 to 1.61)	174	1.35 (0.95 to 1.93)	1.30 (0.88 to 1.90)
Hispanic	79	0.88 (0.53 to 1.46)	0.88 (0.52 to 1.49)	136	0.85 (0.57 to 1.28)	0.80 (0.52 to 1.24)
Asian	35	1.28 (0.63 to 2.61)	1.13 (0.56 to 2.29)	72	1.16 (0.67 to 2.01)	1.08 (0.59 to 1.97)
Age at Diagnosis						
< 65 years	337	1.37 (1.02 to 1.82)	1.30 (0.90 to 1.89)	559	2.26 (1.67 to 3.04)	2.32 (1.58 to 3.41)
65 years or older	671	ref	ref	808	ref	ref
Insurance						
Medicare and Private	357	0.77 (0.55 to 1.07)	0.90 (0.59 to 1.36)	382	0.82 (0.58 to 1.16)	1.46 (0.95 to 2.24)
Medicare only	154	0.73 (0.48 to 1.12)	0.87 (0.54 to 1.42)	292	0.42 (0.28 to 0.63)	0.75 (0.47 to 1.19)
Private only	331	ref	ref	512	ref	ref
Medicaid or None	119	0.88 (0.56 to 1.39)	0.95 (0.59 to 1.55)	154	0.90 (0.54 to 1.49)	0.97 (0.56 to 1.67)
Other or Unknown	47	0.29 (0.14 to 0.63)	0.33 (0.15 to 0.73)	27	0.34 (0.14 to 0.81)	0.48 (0.21 to 1.13)

Abbreviations: uOR = unadjusted odds ratio; aOR = adjusted odds ratio

*Adjusted for race and variables significant in univariate analysis (sex, age group, insurance, and treatment received)

Table 4:

Frontline CLL treatment regimens ranked by prevalence and stratified by diagnosis year

	2008		2014	
	Regimen	**N (%*)**	**Regimen**	**N (%*)**
All Cases				
Most common	FCR	67 (25.8)	BR	133 (35.5)
2nd most common	R monotherapy	35 (14.7)	R monotherapy	58 (14.8)
3rd most common	FR	30 (10.2)	FCR	52 (11.9)
4th most common	Chlorambucil +/−	26 (9.5)	Ibrutinib	34 (8.4)
Age < 70 at diagnosis				
Most common	FCR	53 (40.7)	BR	89 (42.5)
2nd most common	FR	20 (13.2)	FCR	51 (19.9)
3rd most common	R monotherapy	11 (7.7)	Ibrutinib	23 (10.5)
4th most common	CVP +/− R	<11	R monotherapy	26 (9.8)
Age ≥ 70 at diagnosis				
Most common	R monotherapy	24 (21.9)	BR	44 (25.4)
2nd most common	Chlorambucil +/−	17 (12.8)	R monotherapy	32 (22.2)
3rd most common	Other	13 (11.2)	Other	11 (12.6)
4th most common	R + anything else	<11	Obinutuzumab	16 (11.4)
Charlson Comorbidity Score = 0				
Most common	FCR	56 (31.8)	BR	96 (39.1)
2nd most common	FR	25 (12.7)	FCR	41 (13.7)
3rd most common	R monotherapy	20 (11.6)	R monotherapy	39 (13.0)
4th most common	Chlorambucil +/−	16 (7.8)	Ibrutinib	24 (8.9)
Charlson Comorbidity Score 1 or more				
Most common	R monotherapy	15 (21.5)	BR	37 (28.0)
2nd most common	Chlorambucil +/−	<11	R monotherapy	18 (18.7)
3rd most common	FCR	<11	Obinutuzumab	13 (12.8)
4th most common	CVP +/− R	<11	Ibrutinib	<11

Abbreviations: CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide, and rituximab; BR, bendamustine and rituximab; R, rituximab; FR, fludarabine and rituximab; CVP, cyclophosphamide, vincristine, and prednisone.

*Percentages are weighted by sampling fraction to reflect the SEER 14 population from which the data was obtained

To protect patient confidentiality only the 4 most common regimens are presented and any cell sizes <11 have been suppressed.

Table 5.

Receipt of testing and CLL treatments by teaching hospital status and diagnosis year

	2008			2014		
	Non-Teaching Hospital	Teaching Hospital		Non-Teaching Hospital	Teaching Hospital	
	N (%*)	N (%*)	p value	N (%*)	N (%*)	p value
Total	476	528		585	767	
FISH performed			0.159			0.011
Performed	179 (41.5)	253 (46.1)		294 (45.7)	443 (55.2)	
Not Performed / Unknown	297 (58.5)	275 (53.9)		291 (54.3)	324 (44.8)	
Karyotype performed			0.521			0.283
Performed	139 (33.8)	197 (35.8)		204 (33.6)	294 (37.2)	
Not Performed / Unknown	337 (66.2)	331 (64.2)		381 (66.4)	473 (62.8)	
Mutated variable immunoglobulin heavy chain			0.366			0.051
Performed	30 (5.5)	33 (6.8)		67 (8.7)	101 (12.1)	
Not Performed / Unknown	446 (94.5)	495 (93.2)		518 (91.3)	666 (87.9)	
Bone Marrow Biopsies			0.014			0.101
Performed	231 (50.3)	233 (42.1)		251 (42.2)	281 (36.4)	
Not Performed / Unknown	245 (49.7)	295 (57.9)		334 (57.8)	486 (63.6)	
Lymph Node Biopsies			0.543			0.307
Performed	25 (5.4)	27 (4.5)		157 (25.2)	224 (28.3)	
Not Performed / Unknown	451 (94.6)	501 (95.5)		428 (74.8)	543 (71.7)	
CLL Treatments**	**Regimen; (%*)**	**Regimen; (%*)**		**Regimen; (%*)**	**Regimen; (%*)**	
Frontline regimens						
Most common	FCR; (22.5)	FCR; (29.7)		BR; (47.3)	BR; (25.5)	
2nd most common	R; (19.0)	Other; (13.2)		R; (12.6)	R; (16.6)	
3rd most common	Chl +/−; (11.0)	FR; (12.3)		Ibrutinib; (8.2)	FCR; (16.0)	
4th most common	CVP +/− R; (9.1)	R; (9.2)		FCR: (6.7)	Ibrutinib; (8.7)	
Use of New Agents (obinutuzumab, ibrutinib, idelalisib)				**N (%*)**	**N (%*)**	**p value**
No				144 (86.3)	180 (82.9)	0.453

	2008			2014		
	Non-Teaching Hospital	Teaching Hospital		Non-Teaching Hospital	Teaching Hospital	
	N (%*)	N (%*)	p value	N (%*)	N (%*)	p value
Yes				27 (13.7)	35 (17.1)	

Abbreviations: FISH, fluorescent in situ hybridization; CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide, and rituximab; BR, bendamustine and rituximab; R, rituximab; FR, fludarabine and rituximab; Chl, chlorambucil; CVP, cyclophosphamide, vincristine, and prednisone

*Percentages are weighted by sampling fraction to reflect the SEER 14 population from which the data was obtained

**Among those who received systemic treatment

***19 cases had the type of treating facility coded as unknown and are omitted from the table