Assessing the Effectiveness of Treatment Sequences for Older Patients With High-risk Follicular Lymphoma With a Multistate Model

Caglar Caglayan, *Georgia Institute of Technology*
Hiromi Terawaki, *Emory University*
Turgay Ayer, *Georgia Institute of Technology*
Jordan S. Goldstein, *Emory University*
Ashish Rai, *American Cancer Society, Inc.*
Qiushi Chen, *Massachusetts General Hospital*
Christopher Flowers, *Emory University*

Journal Title: Clinical Lymphoma, Myeloma and Leukemia
Volume: Volume 19, Number 5
Publisher: Elsevier: 12 months | 2019-05-01, Pages 300-+
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/j.clml.2018.12.019
Permanent URL: https://pid.emory.edu/ark:/25593/tqzsb

Final published version: http://dx.doi.org/10.1016/j.clml.2018.12.019

Copyright information:

HHS Public Access

Author manuscript

Clin Lymphoma Myeloma Leuk. Author manuscript; available in PMC 2019 June 07.

Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2019 May ; 19(5): 300–309.e5. doi:10.1016/j.clml.2018.12.019.

Assessing the Effectiveness of Treatment Sequences for Older Patients With High-risk Follicular Lymphoma With a Multistate Model

Çağlar Çağlayan[1], **Hiromi Terawaki**[2], **Turgay Ayer**[1], **Jordan S. Goldstein**[2], **Ashish Rai**[3], **Qiushi Chen**[4], and **Christopher Flowers**[2]

[1]H. Milton Stewart School of Industrial and Systems Engineering, Georgia Institute of Technology, Atlanta, GA

[2]Winship Cancer Institute of Emory University, Atlanta, GA

[3]American Cancer Society, Inc, Atlanta, GA

[4]Institute for Technology Assessment, Massachusetts General Hospital, Boston, MA

Abstract

Using a large data set, the present survival analysis study assessed the effect of sequential therapies for patients with follicular lymphoma aged ≥ 65 years using a multistate model. We found that rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine in any line of therapy improved overall survival.

Background: Disease progression within < 2 years of initial chemoimmunotherapy and patient age > 60 years have been associated with poor overall survival (OS) in follicular lymphoma (FL). No standard treatment exists for these high-risk patients, and the effectiveness of sequential therapies remains unclear.

Patients and Methods: We studied the course of FL with first-, second-, and third-line treatment. Using large population-based data, we identified 5234 patients with FL diagnosed in 2000 to 2009. Of these patients, 71% had received second-line therapy < 2 years, and 29% had received no therapy after first-line therapy, with a median OS of < 3 years. Treatment included rituximab, R-CVP (rituximab, cyclophosphamide, vincristine), R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine), R-Other (other rituximab-containing), and other regimens. The Aalen-Johansen estimator and Cox proportional hazards models were used to quantify the outcomes and assess the effects of the clinical and sociodemographic factors.

Results: R-CHOP demonstrated the most favorable 5-year OS among first- (71%), second- (55%), and third-line (61%) therapies. First-line R-CHOP improved OS (hazard ratio [HR], 0.57;

Address for correspondence: Çağlar Çağlayan, MS, H. Milton Stewart School of Industrial and Systems Engineering, Georgia Institute of Technology, 755 Ferst Drive Northwest, Room 321, ISyE Main Building, Atlanta, GA 30332, ccaglayan6@isye.gatech.edu.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

The supplemental figures and tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clml.2018.12.019.

95% confidence interval [CI], 0.50–0.64) and reduced the mortality risks after first-line (HR, 0.60; 95% CI, 0.47–0.77), second-line (HR, 0.40; 95% CI, 0.29–0.53), and third-line (HR, 0.63; 95% CI, 0.53–0.76) treatments. B-symptoms, being married, and histologic grade 1/2 were associated with the use of earlier second-line therapy. Early progression from second- to third-line therapy was associated with poor OS. The repeated use of R-CHOP or R-CVP as first- and second-line treatment yielded high 2-year mortality rates (R-CHOP + R-CHOP, 17.3%; R-CVP + R-CVP, 21.1%).

Conclusion: Our multistate approach assessed the effect of sequential therapy on the immediate and subsequent treatment-line outcomes. We found that R-CHOP in any line improved OS for patients with high-risk FL.

Keywords

Follicular lymphoma; High-risk; Multistate model; Survival prediction; Treatment-related mortality

Introduction

Follicular lymphoma (FL) is the most common indolent and the second-most common non-Hodgkin lymphoma—accounting for ~20% to 25% of all lymphomas in Western countries.[1,2] For most patients, FL will be an incurable disease characterized by indolent behavior, with an initial period of observation followed by a favorable response to the initial therapy. Most patients with newly diagnosed FL treated with rituximab alone or rituximab plus chemotherapy will experience prolonged progression-free survival (PFS) and overall survival (OS). However, the FL of some patients will undergo transformation to more aggressive histologic grades.[3] Also, ~20% will experience progression of disease (PD) within 2 years of first-line chemoimmunotherapy, irrespective of the treatment choice.[4]

Large randomized studies have consistently shown patients with FL and early PD will have poorer OS compared with those patients without relapse within the first 2 years.[5–7] Consistent with these trials, an analysis of data from the National LymphoCare cohort study in the United States involving 588 patients with stage II-IV FL treated with first-line rituximab plus chemotherapy showed that 19% had developed a relapse within 2 years of diagnosis.[4] In addition, OS was markedly reduced in the group with early PD, with a 5-year survival rate of 50% from the 2-year risk-defining progression event compared with 90% for patients without early PD. Validation of these data in an independent cohort of patients with FL for Iowa/Mayo confirmed the poor 5-year OS for patients with early relapse.[4] In addition to early PD, advanced age also has been identified as a high-risk factor for a poor clinical course of FL and worse survival.[8–10] In particular, age > 60 years has been shown to be a key adverse prognostic factor associated with poorer OS and PFS and is a component of the FL international prognostic index.[11–13]

Limited data are available regarding the outcomes associated with the sequencing of first-, second-, and third-line therapy for FL. The sequence remains important because most patients will develop relapse and will require sequential treatment. Moreover, no study has reported on the effect of sequential therapy among the most vulnerable patients with FL—

those aged > 60 years and requiring a second treatment within 2 years of the initial therapy. We developed a continuous-time multistate model to capture the clinical course of FL for older patients with high-risk FL and conducted a multistate survival analysis to examine the outcomes associated with first-, second-, and third-line therapy and to assess the effects of sociodemographic and clinical factors on the outcomes at each treatment line and OS.

Patients and Methods

Our multistate model consisted of 3 treatment states (alive after first-, second-, and third-line treatment) and an absorbing health state "dead" (Figure 1). The patients with FL entered a treatment state with the initiation of the corresponding treatment line and departed when either they had died or their next treatment had been initiated. We used the Aalen-Johansen estimator,[14] a generalization of the Kaplan-Meier estimator,[15] to assess the likelihood of a patient being in 1 of the 4 clinical states at a given time. The Aalen-Johansen estimator is a convenient and reliable (nearly unbiased) nonparametric estimator for multistate models. It does not assume any form on probability distributions and can cope with the censored observations that exist in clinical data. It was mathematically shown that the Aalen-Johansen estimator is the maximum likelihood estimator of multistate models[16,17] and provides consistent estimates for both Markov and non-Markov models.[18]

We used multivariable Cox proportional hazard regression models to assess the influence of clinical and sociodemographic factors at each state transition. The Cox model is a semiparametric model that has been commonly used in clinical studies to examine the association between covariates and the time of the event of interest.[19,20] First, we constructed a multivariable Cox regression model for the conventional OS model with 2 model states, "alive after initial treatment" and "dead," and analyzed the effect of the predictors on OS. Next, for a more comprehensive analysis, we fit a multivariable Cox proportional hazard regression model to each transition between the model states of the multistate model and identified significant risk factors affecting the time and rate of each clinical event, such as death, and the initiation of a subsequent therapy.

Patients, Data Source, and Variables

Data from the Surveillance, Epidemiology, and End Results (SEER) 2000 to 2009 registry, which has been linked with the Medicare claims data through 2011, were used to identify patients with a histologically confirmed first primary diagnosis of FL using the International Classification of Diseases (ICD) for Oncology, 3rd edition, histology codes.[21] The SEER program is a National Cancer Institute — sponsored epidemiologic surveillance system of population-based tumor registries that routinely seek to collect demographic and clinical information on all incident cases occurring in the SEER areas.[22] Medicare is the primary health insurer for 93% of the US population aged ≥ 65 years. Medicare claims data contain information collected to cover health care services provided to Medicare beneficiaries. Because the median age at diagnosis for patients with FL is > 65 years, the SEER-Medicare data offer a valuable resource to examine FL patterns of care and outcomes.

The SEER-Medicare data set included a total of 8411 patients with FL aged ≥ 65 years. After our examination for eligibility, 3177 patients were excluded for the following reasons:

insufficient data (n = 676), diagnosis before 2000 (n = 1342), no treatment received after the diagnosis (n = 821), and PD > 2 years after the initial treatment (n = 338; Figure 2). All 5234 patients included in the present analysis had an advanced age > 65 years, a high-risk factor for poor PFS and OS[11–13]; had received at least first-line therapy after diagnosis in the era of routine first-line rituximab and rituximab plus chemotherapy (after 2000); and had either experienced early PD < 2 years after first-line therapy (71%), a risk factor for poorer OS[4] or experienced a median OS of < 3 years (29%).

Starting with their diagnosis, the patients were observed until death or the end of the follow-up period (December, 31, 2009 for SEER and December 31, 2011 for Medicare data). We used Medicare as the primary source for the time of death information and adjusted the missing entries using the SEER data, assuming the 15th day of the month as the time of death. The primary variables of interest were the receipt of first-, second-, and third-line treatment and the OS with each line of treatment. We identified FL-directed treatment strategies using the ICD (9th revision, clinical modification, diagnosis; and 9th revision, clinical modification, procedural), Current Procedural Terminology, Healthcare Common Procedure Coding System, and revenue centers codes [22] on inpatient, outpatient, and physician claims. We grouped treatments into 5 main categories as follows: (1) rituximab with or without radiotherapy; (2) R-CVP (rituximab, cyclophosphamide, vincristine); (3) R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine); (4) R-Other (rituximab with other chemotherapy combinations); and (5) Non-R (treatments that did not contain rituximab). The data also included patients with unknown treatments. When we investigated the optimal first-, second-, and third-line therapies, we presented the results for the treatment groups rituximab, R-CVP, R-CHOP, and R-Other. When we examined the effects of the clinical and sociodemographic risk factors on the clinical course of FL, we considered all patients, including those patients who had received Non-R and unknown treatments. To adjust for the use of rituximab maintenance therapy after induction, we classified a treatment as involving rituximab maintenance if rituximab alone had been received within 180 days of the previous treatment and > 1 dose of rituximab treatment had been given (Figure 2).

Patient age, race, sex, marital status, region demographic data (Northeast, Midwest, South, or West), residency demographic data (metropolitan, urban, or rural), and census tract-level characteristics (maximum education level attained) were identified from the SEER data for each patient. FL histologic features, FL grade (1/2, or 3), extranodal primary site of involvement, and the presence of B-symptoms were also recorded from SEER data. A history of anemia, poor performance status, and Deyo modification of the Charlson comorbidity index (CCI) were derived from Medicare data using our previous approach.[23,24]

Results

We assessed the SEER-Medicare data for 8411 patients for eligibility and included 5234 patients, with a diagnosis of FL from 2000 to 2009, in the present study (Figure 2). Of these patients, 71% had received a second-line therapy within 2 years of diagnosis, and 29% had received no further therapy after their initial therapy and had experienced a median OS of < 3 years. All patients were aged > 65 years, the mean age was 76 years, and median duration

from diagnosis to first-line treatment was 1.37 months (95% confidence interval [CI], 1.33–1.43). The baseline patient characteristics stratified by treatment type are listed in Table 1.

In the present FL population enriched for patients with early PD, 1219 had received rituximab alone, 620 R-CVP, 894 R-CHOP, and 432 R-Other as first-line therapy, and 322 patients had received rituximab maintenance therapy after first-line treatment. R-CHOP achieved the highest survival rates at 2 and 5 years among the first-line treatments (76% and 46% for rituximab, 82% and 55% for R-CVP, 84% and 71% for R-CHOP, and 74% and 54% for R-Other, respectively; Figure 3). R-CHOP as second- and third-line therapies was also associated with the most favorable 5-year OS rates after the initiation of second- and third-line treatments (50% and 49% for rituximab, 47% and 38% for R-CVP, 55% and 61% for R-CHOP, and 47% and 46% for R-Other as second- and third-line therapies, respectively; Supplemental Figures 1 and 2; available in the online version). Consistent with these findings, the median OS from the initiation of the corresponding treatment was the highest for R-CHOP patients at any treatment line and was 36.3 months (95% CI, 33.7–38.7) for first-line R-CHOP, 34.1 months (95% CI, 28.6–37.9) for second-line R-CHOP, and 40.4 months (95% CI, 33.5–45.7) for third-line R-CHOP therapy (Table 2).

R-CHOP had the greatest effect on OS when provided as first-line therapy. For patients receiving first-line R-CHOP, followed by 2 other therapies (R-CHOP + X + X), the mortality rate at 2 years after first-, second-, and third-line therapy was 10.9%, 13.8%, and 17.8%, respectively (Table 3). The corresponding mortality rates for second-line R-CHOP (X + R-CHOP + X) were 18.0%, 20.8%, and 23.7%, and for third-line R-CHOP (X + X + R-CHOP) were 25.5%, 31.1%, and 34.0% when R-CHOP was combined with any 2 other regimens. During the course of the sequential treatments, first-line R-CVP followed by R-CHOP also was a particularly favorable combination, with no deaths within 24 months of initiating first-line therapy (Table 4). The patients who had received R-Other as first-line therapy in this cohort had poorer outcomes with all second-line regimens if they had received a (subsequent) second-line therapy (Table 4).

Compared with other regimens, first-line R-CHOP was effective across all age subgroups. Among the first-line R-CHOP patients, the 5-year OS rates were 0.70 for age 66 to 70 years, 0.71 for age 71 to 75 years, 0.75 for age 76 to 80 years, and 0.66 for age ≥ 81 years. In contrast, the 5-year OS rates were lower for patients receiving other rituximab-based regimens, including rituximab, R-CVP, or R-Other as first-line therapy. For these groups of patients, the 5-year OS rates were 0.52 for age 66 to 70 years, 0.52 for age 71 to 75 years, 0.49 for age 76 to 80 years, and 0.48 for age ≥ 81 years. In terms of comorbid conditions, first-line R-CHOP was slightly less effective for patients with a CCI > 1, for whom the 5-year OS rates were 0.71 for CCI ≤ 1 and 0.66 for CCI > 1. The FL stage affected the performance of first-line R-CHOP, with the 5-year OS rate decreasing from 0.75 (for stage ≤ 2) to 0.66 for stage > 2. Although moderate, the histologic type was also influential in the effectiveness of R-CHOP. The 5-year OS rates were 0.74 for FL grade 1/2 and 0.70 for grade 3. The factors affecting the outcomes for R-CHOP were not as influential in patients receiving front-line rituximab treatment. The effect of age, CCI, stage, grade, and performance status on the 5-year OS rates among patients receiving rituximab only as their first-line therapy were as follows: 0.48 for age 66 to 70 years, 0.50 for age 71 to 75 years,

0.47 for age 76 to 80 years, and 0.51 for age ≥ 81 years; 0.49 for CCI > 1 and 0.49 for CCI ≤ 1; 0.48 for FL stage ≤ 2 and 0.51 for FL stage > 2; 0.50 for grade 1/2 and 0.49 for grade 3; and 0.50 for favorable performance status and 0.48 for unfavorable performance status.

A total of 3734 patients had received a second-line therapy, and 65% of these patients had received a subsequent third-line therapy within 2 years of their second-line therapy. The therapy regimens included rituximab for 750, R-CVP for 198, R-CHOP for 286, and R-Other for 356. For these patients, the empirical 2- and 5-year OS rates after second-line therapy were 83% and 55% for rituximab, 76% and 45% for R-CVP, 77% and 55% for R-CHOP, and 75% and 45% for R-Other, respectively.

Multivariable Cox regression models revealed that the presence of B-symptoms, being married, and histologic grade 1/2 FL were associated with earlier initiation of the second-line therapy, and age > 85 years was associated with an elevated risk of death after first-line treatment (Supplemental Table 1; available in the online version). The Cox models also substantiated that R-CHOP in any treatment line improved OS by reducing the rate of death after first-, second- and third-line treatment. Compared with the baseline treatment group of rituximab, first-line R-CHOP reduced the risk of death after first-line treatment (hazard ratio [HR], 0.60; 95% CI, 0.47–0.77), and improved OS after any subsequent second-line treatment (HR, 0.40; 95% CI: 0.29–0.53) and third-line treatment (HR, 0.63; 95% CI, 0.53–0.76). Second- and third-line R-CHOP treatment had a similar positive effect on OS. The mortality risk was reduced by second-line R-CHOP, with a HR of 0.61 (95% CI, 0.44–0.84) after second-line therapy and a HR of 0.80 (95% CI, 0.66–0.96) after any third-line treatment. The mortality risk was also reduced by third-line R-CHOP (HR, 0.81; 95% CI, 0.66–1.00).

As might be expected, R-CHOP followed by second-line R-CHOP yielded unfavorable clinical outcomes. Among all the patients who had received first-line R-CHOP and who had also received second-line therapy, the 2-year mortality rates were as followed: R-CHOP followed by rituximab, 9.7%; R-CHOP followed by R-CVP, 8%; R-CHOP followed by R-CHOP, 17.3%; and R-CHOP followed by R-Other, 12.3% (Table 4). Similarly, the repeated use of R-CVP (ie, R-CVP + R-CVP) yielded adverse outcomes with the highest 2-year mortality rate of 21.1% compared with other clinical scenarios, where first-line R-CVP was followed by another second-line regimen: R-CVP + rituximab, 5.7%; R-CVP + R-CHOP, 0%; and R-CVP + R-Other, 14% (Table 4). In contrast, R-CHOP followed by R-CVP and R-CVP followed by R-CHOP both resulted in low 2-year mortality rates (0% and 8%, respectively; Table 4).

Discussion

Currently, no standard of care is available for the initial treatment after the diagnosis of FL in the United States. The management options have included watchful waiting, single-agent therapy, combination chemotherapy with immunotherapy, and radiotherapy.[25] For instance, the initial first-line strategies among 2728 patients reported by National LymphoCare cohort study included watchful waiting for 17.7%, rituximab alone for 13.9%, a clinical trial for 6.1%, radiotherapy for 5.6%, chemotherapy for 3.2%, and rituximab with chemotherapy for

51.9%.[25] Since that report, rituximab plus bendamustine and maintenance rituximab after chemoimmunotherapy have emerged as other common first-line approaches.[5–7] However, no treatment strategy has demonstrated superior outcomes compared with all alternatives. The effects of the clinical and biologic data or functional imaging findings on FL outcomes have been analyzed in a number of studies,[6,26–28] and patients with early relapse have been significantly more likely than patients without early PD to have high FL International Prognostic Index scores ($P = .007$)[4] and to have worse OS. At present, identifying the subset of patients at the greatest risk of early PD and the optimal treatment strategies for these patients remain unmet clinical needs.[3] However, few studies have examined the patterns of care, effect of certain regimens across lines of therapy, or the optimal therapy sequence for patients with FL who have experienced early PD.

In the present population of 5234 patients, enriched for older patients with FL with an early initiation of second-line therapy, our analysis revealed that R-CHOP for any treatment line was associated with the highest OS, and the most favorable effect was achieved when R-CHOP was provided as first-line therapy. However, as might be expected, R-CHOP followed by second-line R-CHOP yielded unfavorable clinical outcomes. One possible explanation could be the anthracycline toxicity due to doxorubicin. Anthracycline-containing regimens have been associated with toxicities, including myelosuppression, mucositis, febrile neutropenia, and cardiomyopathy, especially in older patients, such as the patients included in our data set. Older individuals with lymphoma have been shown to be especially vulnerable to cardiac and hematologic toxicity with anthracycline-based therapies.[29,30] A second explanation would be the development of drug resistance with the chemotherapy rechallenge.[31] Studies on the efficacy of anthracycline rechallenge have focused on breast cancer, and the findings have remained inconclusive.[32] Drug resistance would also explain the unfavorable outcomes seen with repeat use of R-CVP (Table 4). The issue of suboptimal outcomes with the repetitive use of the same regimen, R-CHOP and R-CVP in particular, might be addressed by using either R-CHOP or R-CVP as the first-line treatment and the other as second-line treatment because such treatment sequences have resulted in low 2-year mortality rates in our analysis of the SEER-Medicare data set.

Our study had some limitations. First, we analyzed the effect of first-, second-, and third-line FL treatment and other factors on OS. A more in-depth analysis could assess the effect of these factors specifically on FL-associated mortality using the same multistate framework but distinguishing “death due to FL” and “death from other causes” if the data permitted. Second, the population examined was older patients with FL that had been enriched for high-risk patients. Accordingly, the findings might not be directly generalizable to younger or average-risk patients. Third, novel therapies have been developed for relapsed FL, including bendamustine,[33] obinotuzumab,[34] lenalidomide,[35,36] ibrutinib,[37] and idelalisib,[38–40] which were not directly assessed in the present analysis of patients with a diagnosis of with FL from 2000 through 2009. Although some of these agents were included in the category of R-Other (Supplemental Table 3; available in the online version), these interventions were poorly represented in the present data set and will likely effect future outcomes.

Other data-related limitations included that 632 first-line (12%), 552 second-line (15%), and 430 third-line (17%) treatments were unidentified owing to data limitations. Furthermore, despite our efforts to adjust for the use of rituximab maintenance therapy, we could have had some patients for whom our method failed to correctly categorize the sequence of treatments owing to the limitations of the SEER-Medicare data set. Just as with any observational study, the lack of selection criteria for the choice of R-CHOP and other therapies was another limitation of the SEER-Medicare data set. Although we conducted several multivariable Cox regression analyses to assess the effectiveness of R-CHOP and found that the findings were robust and could not be attributed to another covariate, we could only account for the factors that were available in the data set. The Cox models accounted for age, gender, comorbidities, FL prognostic factors, and other demographic covariates known to influence the outcomes in FL. However, additional unmeasured factors could also have influenced the treatment selection and confounded the assessment of the relationship between treatments and outcomes. Although we performed a SEER population-based study, linkage with the Medicare claims yielded a cohort with a mean age of 76 years. Thus, caution must be exercised when interpreting these findings for clinical practice, because individual patient characteristics, such as the existence of comorbidities, will influence the selection and performance of treatments strategies, especially for older individuals. In these analyses, we adjusted for comorbidities using the CCI. However, other unmeasured comorbidities could have influenced the practice patterns and outcomes. Moreover, the lack of tumor size measures or tumor size-related indications for treatment, such as the Groupe d'Etude des Lymphomes Folliculaires criteria,[41] in the SEER registry or Medicare claims data sets prevented us from analyzing the effect of tumor burden on outcomes. The inclusion of such information in disease-specific clinical data collection in cancer registries would enable further analyses and improve the clarity of the findings from such studies.

Previous predictive models have focused on the effects of a single line of therapy on a single outcome of interest such as PFS or OS. However, our model allows us to untangle the effects of first-line and additional therapies on subsequent treatment progression and factors pertaining to all-cause death. Knowledge regarding the predictive factors for an earlier transition to the next line of treatment would provide clinicians with more specific information to use in the decision-making process and would be particularly valuable for high-risk, older populations. Age has consistently been an important risk factor for worse FL outcomes,[11,12] and age > 85 years was associated with an elevated risk of death after the initial (first-line) treatment for this high-risk population. In addition, age > 80 years was associated with the earlier initiation of third-line treatment, indicating more rapid PD after second-line therapy for older patients. B-symptoms, as expected, were associated with worse OS[12] and with earlier transitions between therapies. In contrast to previous studies that identified being married as a significant predictor of improved outcomes in those with FL,[42] we found that married status predicted for an earlier initiation of second-line therapy.

Although other analyses have documented the poor outcomes associated with early PD after first-line chemoimmunotherapy,[4] the present study is one of the first to indicate in a large data set that early PD from second- to third-line therapy is also associated with poor 2- and 5-year OS. However, we acknowledge that our study selected for patients experiencing early PD after all first-line therapies compared with relapse after chemoimmunotherapy only.[4]

However, the prognosis for these patient groups is not necessarily the same. National clinical trials are now underway for patients with early progression after first-line therapy and their findings might provide more information on this important issue.

In the present study, we modeled the clinical course of FL using a multistate model and the Aalen-Johansen estimator to estimate the clinical course of FL over time with various treatments. We also used Cox regression models to quantify the effect of sociodemographic and clinical factors. Multistate models offer an ideal framework to accurately analyze survival data with multiple intermediate states and/or multiple endpoints.[43] By capturing different types of events and the relationships between these events separately within the same model, the multistate modeling framework distinguishes the differential effects of baseline clinical factors and subsequent treatment events across lines of care and allowed us to evaluate their distinct influences on the outcomes in more detail. This comprehensive modeling framework was especially important for the accuracy of our study. Examining interdependent clinical events within the same model, such as competing risks of OS (ie, death) and different phases of PFS (ie, across multiple lines of subsequent treatment), address the biases in estimates that have been demonstrated to occur when the events have been examined in isolation.[44–47] Our use of the large SEER-Medicare claims database was also critical for our method because the availability of the large data set enabled us to use a nonparametric method and, hence, avoid potentially unrealistic parametric assumptions on the clinical course of FL over time.

Our study has provided the first attempt to examine multiple clinical states beyond diagnosis for patients with FL using the most contemporary data available in the type of large data set required to perform this type of analysis. However, despite its strengths in conceptual design, analysis, and modeling, our study would have significantly benefited from a data set that included more modern front-line chemoimmunotherapy agents such as bendamustine. For example, data from the BRIGHT study[48] suggested that bendamustine combined with rituximab produced outcomes equivalent to R-CHOP or R-CVP for patients with previously untreated advanced stage FL. In addition, data from the Study Group Indolent Lymphomas[5] suggested that bendamustine and rituximab improved PFS compared with R-CHOP for patients with advanced-stage FL receiving first-line therapy. However, because bendamustine was underrepresented in the present SEER-Medicare data set, we were not able to conduct further analysis on the effectiveness of treatments that include this agent. To the best of our knowledge, no existing resource can provide sufficient detailed information on subsequent lines of therapy after first-line bendamustine plus rituximab treatment and sufficient follow-up to describe the outcomes. However, because large clinical data sets with more contemporary treatment strategies, such as the FLASH (Follicular Lymphoma Analysis of Surrogate Hypothesis) collaboration,[49] are now becoming available, we are optimistic that similar multistate survival analyses will be conducted using these new and richer data sets to produce more insightful results.

Conclusion

We conducted a multistate survival analysis to study the clinical course of FL with first-, second-, and third-line treatments and assess the effect of sequential therapy on the

immediate and subsequent line outcomes. Our analysis revealed that R-CHOP at any line of treatment improved OS, achieving the most favorable effects when given as the first-line therapy. Together, these findings suggest that R-CHOP remains an appropriate comparator for clinical trials involving patients with high-risk FL at any line of therapy compared with rituximab monotherapy, R-CVP, and R-Other. However, caution must be exercised in the generalization of the effectiveness of first-line R-CHOP, because the study population derived from the SEER-Medicare data set, consisting of all patients receiving first-line therapy, was enriched for older high-risk patients with poor FL outcomes (early PD or death).

The multistate model approach allowed for a more detailed analysis of the effect of clinical covariates on the phases of care and ensured model accuracy for distinguishing the endpoints. The utility of this approach is not limited to FL and can be applied to other clinical situations to inform decision-making on the sequences of therapy when longitudinal time-to-event data are available for patient populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research reported in this publication was supported in part by a Burroughs Wellcome Fund Innovation in Regulatory Science Award and National Cancer Institute award (no. K24CA208132 to C.F. and T32CA160040 to H.T.) and the Winship Research Informatics shared resource, a developing core supported by the Winship Cancer Institute of Emory University (grant P30CA138292). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The data were from the Surveillance, Epidemiology, and End Results (SEER)-Medicare and are not owned by the authors of the present study. Data requests will be reviewed by SEER-Medicare and will need to comply with the SEER-Medicare data use agreement. Requests for data should be sent to SEER-Medicare from the US National Cancer Institute webpage or by contacting Elaine Yanisko (Information Management Services, Inc, 3901 Calverton Boulevard, S200, Calverton, MD 20705, or yaniskoe@imsweb.com).

References

1. Tan D, Horning SJ. Follicular lymphoma: clinical features and treatment. Hematol Oncol Clin North Am 2008; 22:863–82. [PubMed: 18954741]
2. Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes [e-pub ahead of print]. CA Cancer J Clin 2019 10.3322/caac.21357. Accessed: May 22, 2018.
3. Casulo C, Nastoupil L, Fowler NH, Friedberg JW, Flowers CR. Unmet needs in the first-line treatment of follicular lymphoma. Ann Oncol 2017; 28:2094–106. [PubMed: 28430865]
4. Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. J Clin Oncol 2015; 33:2516–22. [PubMed: 26124482]
5. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013; 381:1203–10. [PubMed: 23433739]
6. Press OW, Unger JM, Rimsza LM, et al. A comparative analysis of prognostic factor models for follicular lymphoma based on a phase III trial of CHOP-rituximab vs CHOP + 131iodine-tositumomab. Clin Cancer Res 2013; 19: 6624–32. [PubMed: 24130072]

7. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet 2011; 377: 42–51. [PubMed: 21176949]
8. Decaudin D, Lepage E, Brousse N, et al. Low-grade stage III-IV follicular lymphoma: multivariate analysis of prognostic factors in 484 patients—a study of the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1999; 17:2499–505. [PubMed: 10561315]
9. Federico M, Vitolo U, Zinzani PL, et al. Prognosis of follicular lymphoma: a predictive model based on a retrospective analysis of 987 cases. Blood 2000; 95: 783–9. [PubMed: 10648386]
10. Maartense E, Le Cessie S, Kun-Nelemans HC, et al. Age-related differences among patients with follicular lymphoma and the importance of prognostic scoring systems: analysis from a population-based non-Hodgkin's lymphoma registry. Ann Oncol 2002; 13:1275–84. [PubMed: 12181252]
11. Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the International Follicular Lymphoma Prognostic Factor Project. J Clin Oncol 2009; 27:4555–62. [PubMed: 19652063]
12. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004; 104:1259–65.
13. Nooka AK, Nabhan C, Zhou X, et al. Examination of the follicular lymphoma international prognostic index (FLIPI) in the National LymphoCare study (NLCS): a prospective US patient cohort treated predominantly in community practices. Ann Oncol 2012; 24:441–8. [PubMed: 23041589]
14. Aalen O, Johansen S. An empirical transition matrix for non-homogeneous Markov chains based on censored observations. Scand J Statist 1978; 5:141–50.
15. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457–81.
16. Andersen PK, Borgan O, Gill RD, Keiding N. Statistical Methods Based on Counting Processes New York, NY: Springer-Verlag; 1993.
17. Borgan Ø. Aalen-Johansen estimator. In: Armitage P, Cotlon T, eds. Encyclopedia of Biostatistics New York, NY: John Wiley and Sons, Inc; 2005.
18. Datta S, Satten G. Validity of the Aalen-Johansen estimators of stage occupation probabilities and Nelson-Aalen estimators of integrated transition hazards for non-Markov models. Stat Prob Lett 2001; 55:403–11.
19. Cox D Partial likelihood. Biometrika 1975; 62:269–76.
20. Cox D Regression models and life-tables. J Roy Stat Soc B 1972; 34:187–220.
21. World Health Organization. International Classification of Diseases for Oncology, 1st revision 3 ed. Geneva: World Health Organization; 2013.
22. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care 2002; 40(suppl), IV-3–18.
23. Nabhan C, Byrtek M, Rai A, et al. Disease characteristics, treatment patterns, prognosis, outcomes and lymphoma-related mortality in elderly follicular lymphoma in the United States. Br J Haematol 2015; 170:85–95. [PubMed: 25851937]
24. Rai A, Nastoupil LJ, Williams JN, et al. Patterns of use and survival outcomes of positron emission tomography for initial staging in elderly follicular lymphoma patients. Leuk Lymphoma 2017; 58:1570–80. [PubMed: 27830968]
25. Friedberg JW, Taylor MD, Cerhan JR, et al. Follicular lymphoma in the United States: first report of the national LymphoCare study. J Clin Oncol 2009; 27:1202–8. [PubMed: 19204203]
26. Arcaini L, Merli M, Passamonti F, et al. Validation of follicular lymphoma international prognostic index 2 (FLIPI2) score in an independent series of follicular lymphoma patients. Br J Haematol 2010; 149:455–7. [PubMed: 20064149]
27. Meignan M, Cottereau AS, Versari A, et al. Baseline metabolic tumor volume predicts outcome in highetumor-burden follicular lymphoma: a pooled analysis of three multicenter studies. J Clin Oncol 2016; 34:3618–26. [PubMed: 27551111]

28. Pastore A, Jurinovic V, Kridel R, et al. Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. Lancet Oncol 2015; 16:1111–22. [PubMed: 26256760]
29. Davis CC, Cohen JB, Shah KS, et al. Efficacy and tolerability of anthracycline-based therapy in elderly patients with diffuse large B-cell lymphoma. Clin Lymphoma Myeloma Leuk 2015; 15:270–7. [PubMed: 25704479]
30. Muss HB, Berry DA, Cirrincione C, et al. Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B experience. J Clin Oncol 2007; 25:3699–704. [PubMed: 17704418]
31. Kuczynski EA, Sargent DJ, Grothey A, Kerbel RS. Drug rechallenge and treatment beyond progression—implications for drug resistance. Nat Rev Clin Oncol 2013; 10:571–87. [PubMed: 23999218]
32. Palmieri C, Krell J, James CR, et al. Rechallenging with anthracyclines and taxanes in metastatic breast cancer. Nat Rev Clin Oncol 2010; 7:561–74. [PubMed: 20808300]
33. Friedberg JW, Cohen P, Chen L, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. J Clin Oncol 2008; 26:204–10. [PubMed: 18182663]
34. Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol 2016; 17:1081–93. [PubMed: 27345636]
35. Leonard JP, Jung SH, Johnson J, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance). J Clin Oncol 2015; 33:3635–40. [PubMed: 26304886]
36. Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial. Leukemia 2013; 27:1902–9. [PubMed: 23545991]
37. Ujjani CS, Jung SH, Pitcher B, et al. Phase 1 trial of rituximab, lenalidomide, and ibrutinib in previously untreated follicular lymphoma: Alliance A051103. Blood 2016; 128:2510–6. [PubMed: 27697771]
38. Gopal AK, Kahl BS, de Vos S, et al. PI3Kd inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014; 370:1008–18. [PubMed: 24450858]
39. Gopal AK, Kahl BS, Flowers CR, et al. Idelalisib is effective in patients with high-risk follicular lymphoma and early relapse after initial chemoimmunotherapy. Blood 2017; 129:3037–9. [PubMed: 28325864]
40. Salles G, Schuster SJ, de Vos S, et al. Efficacy and safety of idelalisib in patients with relapsed, rituximab- and alkylating agent-refractory follicular lymphoma: a subgroup analysis of a phase 2 study. Haematologica 2017; 102:e156–9. [PubMed: 27979923]
41. Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1997; 15:1110–7. [PubMed: 9060552]
42. Wieduwilt MJ, Tao L, Clarke CA, et al. Impact of marital status on the survival of patients with hematologic malignancies reported to the California Cancer Registry. J Clin Oncol 2016; 34:6555.
43. Andersen PK, Keiding N. Multi-state models for event history analysis. Stat Methods Med Res 2002; 11:91–115. [PubMed: 12040698]
44. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol 2012; 41:861–70. [PubMed: 22253319]
45. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation 2016; 133:601–9. [PubMed: 26858290]
46. Basu S, Tiwari RC. Breast cancer survival, competing risks and mixture cure model: a Bayesian analysis. J R Stat Soc Series A (Stat Soc) 2010; 173:307–29.

47. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 1999; 18:695–706. [PubMed: 10204198]

48. Flinn IW, van der Jagt R, Kahl BS, et al. Open-label, randomized, non-inferiority study of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of advanced indolent NHL or MCL: the BRIGHT study. Blood 2014; 123:2944–52. [PubMed: 24591201]

49. Shi Q, Flowers CR, Hiddeman W, et al. Thirty-month complete response as a surrogate end point in first-line follicular lymphoma therapy: an individual patient-level analysis of multiple randomized trials. J Clin Oncol 2016; 35:552–60. [PubMed: 28029309]

Clinical Practice Points

- No standard treatment is available for patients with high-risk FL, and the effectiveness of sequential therapies remains unclear.
- Using a large data set and a multistate model, the present survival analysis study examined the clinical course of FL with first-, second-, and third-line treatment.
- In the present FL population enriched for patients with early PD from first- to second-line therapy, B-symptoms, being married, and histologic grade 1/2 were associated with earlier initiation of second-line therapy.
- Early progression from second- to third-line therapy was associated with poor OS.
- R-CHOP at any treatment line improved OS, achieving the most favorable effect when provided as first-line therapy.
- Our findings suggest that R-CHOP remains an appropriate comparator for clinical trials involving patients with high-risk FL at any line of therapy compared with rituximab monotherapy, R-CVP, and other rituximab-containing treatments (ie, R-Other).
- Using the same regimen in first- and second-line treatments, in particular R-CHOP + R-CHOP and R-CVP + R-CVP, yielded adverse clinical outcomes with high 2-year mortality rates.

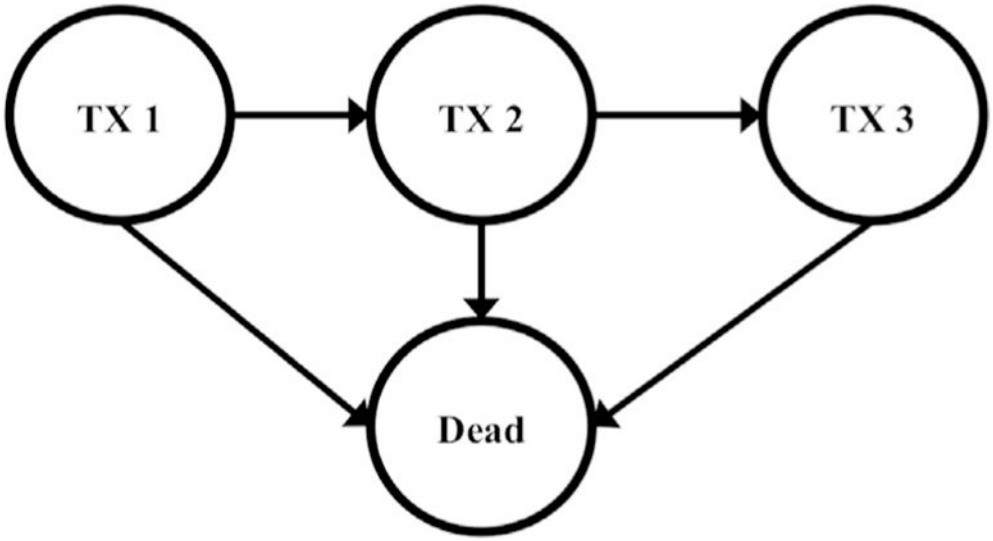

Figure 1.
Multistate Model for the Clinical Course of Follicular Lymphoma
Abbreviation: TX = treatment line.

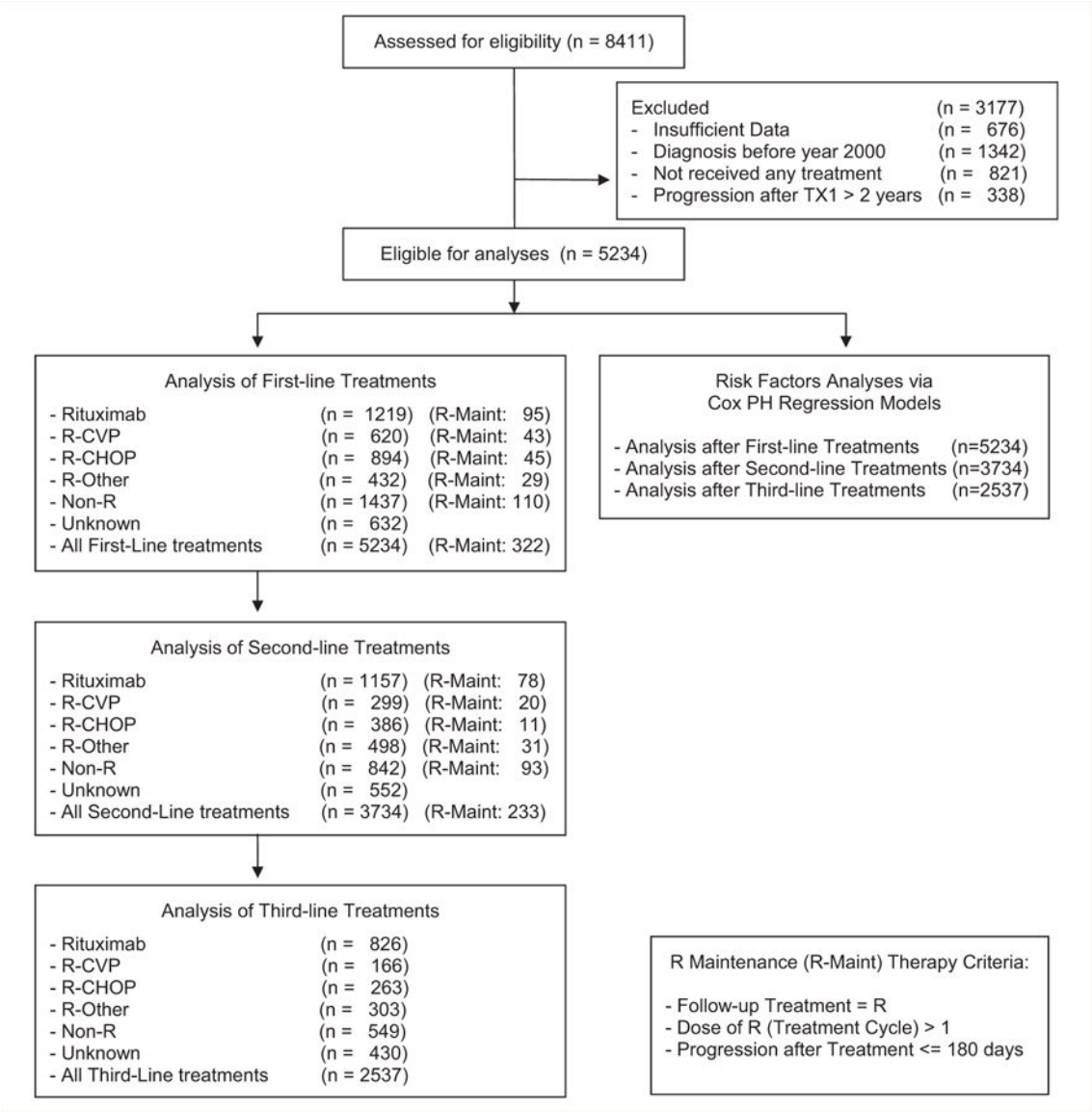

Figure 2.

Consort Flow Diagram Reporting the Number of Patients in Each Analysis

Abbreviations: R-CHOP = rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine; R-CVP = rituximab, cyclophosphamide, vincristine; R-Maint = rituximab maintenance; R-Other = other rituximab-containing regimens; Non-R = treatment without rituximab.

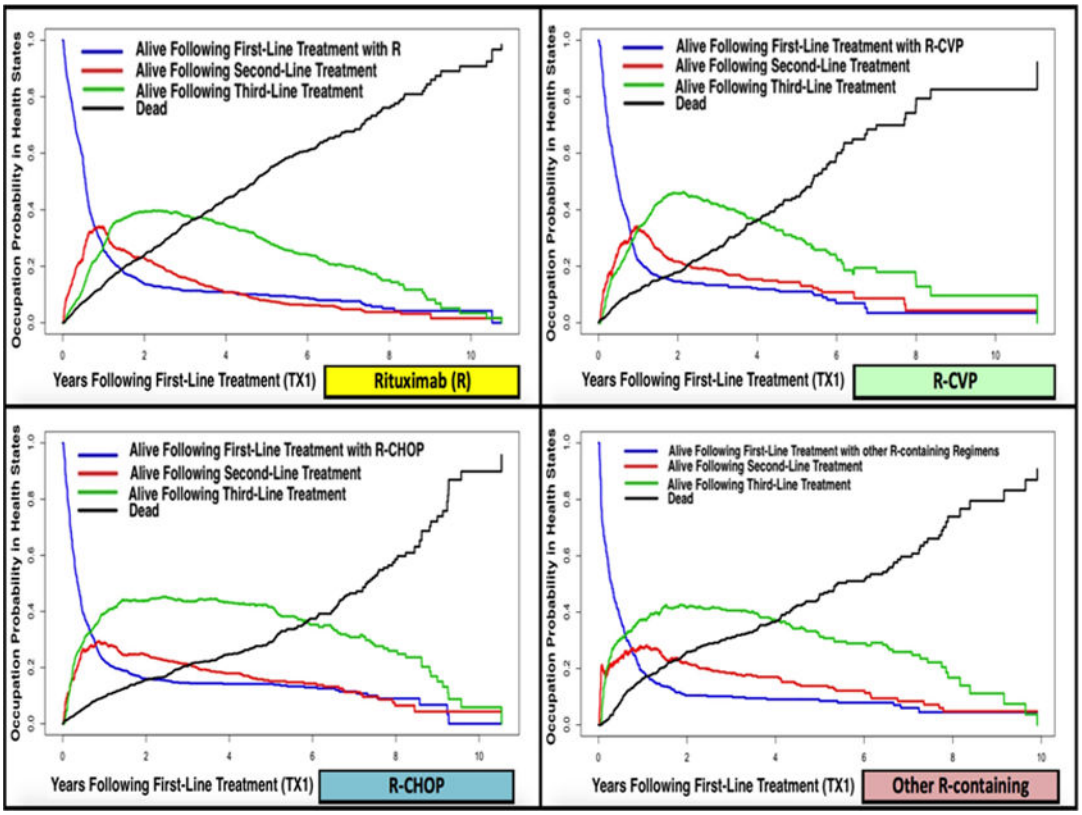

Figure 3.

Graph of Occupation Probabilities Stratified by First-line Treatment

Abbreviations: R-CHOP = rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine; R-CVP = rituximab, cyclophosphamide, vincristine; R-Other = other rituximab-containing regimens.

Table 1

Patient Characteristics for First-line Treatment

Characteristics	Rituximab (n = 219)	R-CVP (n = 620)	R-CHOP (n = 894)	R-Other (n = 432)	All First-Line (n = 5234)
Age at TX1 initiation, y	75.9 ± 6.5	76.2 ± 6.8	75.9 ± 6.6	76.6 ± 6.7	76.0 ± 6.7
Age group at TX1 initiation, y					
66–70	24.2	26.0	24.8	23.6	25.3
71–75	27.0	22.1	28.0	21.8	25.4
76–80	22.3	27.9	21.6	25.2	22.9
≥ 81	26.5	24.0	25.6	29.4	26.5
Race					
White	93.8	93.9	93.1	92.8	93.9
Black	3.8	3.1	2.9	4.6	3.5
Other	2.5	3.1	4.0	2.6	2.6
Sex					
Male	43.2	42.3	42.2	44.4	42.8
Female	56.9	57.7	57.8	55.6	57.2
Marital status					
Married	57.7	57.3	59.2	55.8	57.2
Other	35.9	38.1	34.3	40.5	37.1
Unknown	6.4	4.7	6.5	3.7	5.7
High school education only					
< 25%	29.6	29.4	30.5	27.3	30.0
≥ 25%	66.2	66.1	66.0	69.9	66.1
Unknown	4.2	4.5	3.5	2.8	3.9
FL stage					
I/II	48.7	47.6	44.0	47.7	47.8
III/IV	44.9	47.3	49.2	46.8	46.1
Unknown	6.5	5.2	6.8	5.6	6.1
Primary site of involvement					
Nodal	83.6	84.5	83.1	81.9	83.6

Clin Lymphoma Myeloma Leuk. Author manuscript; available in PMC 2019 June 07.

Characteristics	Rituximab (n = 219)	R-CVP (n = 620)	R-CHOP (n = 894)	R-Other (n = 432)	All First-Line (n = 5234)
Extranodal	16.4	15.5	16.9	18.1	16.5
Charlson comorbidity index					
0	64.6	62.9	63.5	62.0	63.5
1	22.9	23.2	22.9	26.9	23.2
≥ 2	12.6	13.9	13.5	11.1	13.3
Performance status					
Fully active	84.7	84.0	83.0	81.7	83.3
Restricted	15.3	16.0	17.0	18.3	16.7
History of anemia					
Absent	88.2	85.3	85.8	88.9	87.1
Present	11.8	14.7	14.2	11.1	12.9
B symptoms					
Present	12.9	7.7	11.2	12.7	14.3
Absent	3.5	2.3	3.5	3.7	4.5
Unrecorded	83.7	90.0	85.4	83.6	81.2
FL histologic grade					
1 or 2	52.9	52.9	53.0	47.9	53.1
3	18.0	16.9	15.0	19.0	16.4
Not specified	29.1	30.2	32.0	33.1	30.5
Residence					
Metropolitan area	78.0	79.8	74.8	77.6	77.5
Urban or rural	22.0	20.0	25.2	22.5	22.5
Region					
West	21.7	20.8	21.4	22.0	21.5
Northeast	25.8	27.7	22.4	26.4	25.1
Midwest	18.7	23.4	23.0	22.9	22.1
South	33.8	28.1	33.2	28.7	31.4

Data presented as mean ± standard deviation or percentage.

Abbreviations: R-CHOP = rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine; R-CVP = rituximab, cyclophosphamide, vincristine; R-Other = other rituximab-containing regimens; TX1 = first-line treatment.

Table 2

Median Overall Survival Duration From Treatment Initiation

OS From Tx1			OS From Tx2			OS From Tx3		
TX1	**Patients, n**	**Median Duration, mo (95% CI)**	**TX2**	**Patients, n**	**Median Duration, mo (95% CI)**	**TX3**	**Patients, n**	**Median Duration, mo (95% CI)**
Rituximab	1219	33.3 (31.1–35.1)	Rituximab	1157	29.6 (27.9–31.7)	Rituximab	826	25.2 (23.3–27.2)
R-CVP	620	30.7 (28.4–32.1)	R-CVP	299	27.4 (24.0–30.7)	R-CVP	166	26.0 (23.4–30.5)
R-CHOP	894	36.3 (33.7–38.7)	R-CHOP	386	34.1 (28.6–37.9)	R-CHOP	263	40.4 (33.3–45.7)
R-Other	432	34.8 (30.2–39.8)	R-Other	498	28.9 (26.5–33.3)	R-Other	303	28.9 (24.7–35.2)
All, TX1	5234	33.3 (32.2–34.3)	All, TX2	3734	29.6 (28.5–30.8)	All, TX3	2537	25.8 (24.8–26.8)

Abbreviations: CI = confidence interval; OS = overall survival (interval to last follow-up or death); R-CHOP = rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine; R-CVP = rituximab, cyclophosphamide, vincristine; R-Other = other rituximab-containing regimens; TX1 = first-line treatment; TX2 = second-line treatment; TX3 = third-line treatment.

Table 3

Effect of R-CHOP as First-, Second-, or Third-line Therapy on Mortality

Treatment Sequence With R-CHOP Provided as TX1, TX2, or TX3			Patients, n	Death Within 24 mo, %			Total Deaths, %
TX1	TX2	TX3		After TX1	After TX2	After TX3	
R-CHOP	Any TX, except for R-CHOP	Any TX, except for R-CHOP	304	10.9	13.8	17.8	30.9
Any TX, except for R-CHOP	R-CHOP	Any TX, except for R-CHOP	245	18.0	20.8	23.7	43.7
Any TX, except for R-CHOP	Any TX, except for R-CHOP	R-CHOP	106	25.5	31.1	34.0	51.9

Abbreviations: R-CHOP = rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine; TX = treatment; TX1 = first-line treatment; TX2 = second-line treatment; TX3 = third-line treatment.

Table 4

Percentage of Deaths Within 24 Months of First-line Treatment

	TX1, %				
TX2	**Rituximab (n = 219)**	**R-CVP (n = 620)**	**R-CHOP (n = 894)**	**R-Other (n = 432)**	**All TX1 (n = 5234)**
Rituximab (n = 1157)	9.7	5.7	9.7	17.2	12.8
R-CVP (n = 299)	23.4	21.1	8.0	29.0	23.1
R-CHOP (n = 386)	18.9	0.0	17.3	21.2	21.2
R-Other (n = 498)	28.1	14.0	12.3	25.9	22.1
All TX2 (n = 3734)	17.7	12.1	11.7	23.4	20.4

Data presented as percentage.

Abbreviations: R-CHOP = rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine; R-CVP = rituximab, cyclophosphamide, vincristine; R-Other = other rituximab-containing regimens; TX = treatment; TX1 = first-line treatment; TX2 = second-line treatment.