Estimating the Lifetime Treatment Burden of Patients With Follicular Lymphoma: A Retrospective Study Using Real-World Multicenter Data

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ABSTRACT

PURPOSE Although follicular lymphoma is characterized by long natural history and frequent relapses, data on the number of patients receiving subsequent therapy lines are scarce. To perform reliable health economical calculations for various treatment options, data regarding the lifetime number of therapy courses are needed. The purpose of this study was to use real-world data to create a model that could estimate the treatment burden over a 20-year period.

MATERIALS AND METHODS We performed a 20-year simulation on the basis of retrospectively obtained multicenter data of 743 patients with follicular lymphoma. The simulation was carried out in two steps: First, a competing risk model on the basis of Weibull distribution was used to simulate the state transitions from diagnosis onward and from first-line therapy onward. Then, the data were completed by imputing on the basis of the existing data. Completion of data was repeated for 1,000 times to estimate reliability.

RESULTS In 20 years, 97% (2.5-97.5 percentile range: 96%-98%), 66% (61%-70%), 34% (30%-41%), and 15% (9%-18%) of the patients received first-line, second-line, third-line, and fourth-line therapies, respectively. The median number of therapy lines received by each patient was two.

CONCLUSION Despite long remissions, approximately two thirds of the patients receive at least two lines and one-third at least three lines of therapy during their lifetime.

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INTRODUCTION

Follicular lymphoma (FL) is an indolent disease characterized by the responsiveness to initial therapy followed by frequent relapses. Treatment options for FL are increasing rapidly, and novel therapeutics with increased societal costs, such as chimeric antigen receptor T-cell (CAR T-cell) therapy and bispecific antibodies, are being offered to patients with at least two prior lines of systemic therapy.[1,2] However, the number of patients receiving subsequent therapies during the course of the disease remains largely unknown. Some reports of real-life nature have been published but because of relatively short follow-up of these studies, patients with aggressive disease and short response durations are emphasized.[3,4] Because of the favorable prognosis, acquiring true observational data would take nearly 20 years. When the rapid evolution of treatment is considered, such data would already be out of date when it became available. Therefore, the purpose of this retrospective study was to use real-world data to create a model that could estimate the treatment burden with current treatment options over a 20-year period.

MATERIALS AND METHODS

All adult patients with newly diagnosed FL between 1997 and 2016 in seven Finnish and two Spanish institutions (n = 1,045) were considered for inclusion in this study. Exclusion criteria were (1) FL grade 3 or unknown grade, composite histology at diagnosis, or histological transformation before any treatment was given and (2) lack of information in the medical records concerning date/s of diagnosis and/or relapse and/or last follow-up and/or treatments administered, survival status, or cause of death. Finally, 743 patients were included (Fig 1). The study was approved by the Regional Ethics Committee for the Northern Ostrobothnia Hospital District, and the principles of the Declaration of Helsinki were followed.

Patient characteristics, treatment information, disease progression, and death (cause-classified as progressive lymphoma or other) were verified through extensive review of medical records. Date of histopathology report was considered as the date of diagnosis. To realize a simple state distribution plot, the first day of therapy was registered as

CONTEXT

Key Objective

As there are few data on the number of patients with follicular lymphoma receiving subsequent therapy lines during their lifetime, we performed a simulation that could estimate the treatment burden over a 20-year period.

Knowledge Generated

We noticed that in 20 years, approximately two third of the patients received at least two lines, one-third at least three lines, and 15% at least four lines of therapy. Meanwhile, the median number of therapy lines received by each patient was two.

Relevance

These estimates are of great value when introducing novel therapies with increased societal cost: firstly, to estimate the number of candidates for these therapies in different treatment lines, and secondly, to know the lifetime treatment burden with current practices to be able to address the benefits of novel therapies.

the same day of diagnosis or progression in case a therapy was initiated in real life before histological confirmation.

Progression-free survival (PFS) was calculated from the first day of active treatment to the date of progression, the date of death, or the last date of follow-up, whichever occurred first. Subsequent PFS times (PFS2, PFS3) were calculated in a similar manner as PFS, but by considering the follow-up duration from the first day of the second- and third-line treatments. Survival was estimated using the Kaplan-Meier-method.

To estimate the proportion of patients receiving subsequent lines of therapy, we performed a 20-year long simulation on the basis of the study patient cohort. Possible states among patients were defined as diagnosed with FL, first-line therapy/remission, first progression, second-line therapy/remission, second progression, third-line therapy/remission, third progression, subsequent remissions and progressions correspondingly, and finally death from progressive lymphoma and death from other cause (Fig 2). All patients started with the state of FL diagnosis. First, we considered patients who had been diagnosed with FL but had not moved on to the next state. A competing risk model on the basis of the existing data, with the assumption that individual risks follow Weibull distribution, was used to simulate the state transition for these patients. The competing risks were defined as the initiation of first-line therapy, death from progressive lymphoma, and death from other cause. Next, the same approach with the Weibull assumption was used to simulate the transition for patients who had received first-line treatment but had not moved on to the next state, possible states being first progression, death from progressive lymphoma, and death from other cause. The shortest possible time between first-line therapy and transition to next state was assumed to be 28 days.

Finally, we divided the timeline in periods of 30 days and considered patients' states for each period in chronological order from the beginning. If a patient with a not-known state was found, we used discrete semi-Markov transitions in limited time space to complete the data. We searched the data for patients with a known state who had spent at least an equal amount of time in the same previous state as the patient in question. The missing state was then randomly sampled from these control patients from the corresponding time point. Random sampling guaranteed that patients' not-known state was simulated from a distribution corresponding to the data. This approach was repeated until we had simulated observations for each patient for a period of 20 years. Altogether, completion of data was repeated 1,000 times to estimate the reliability. The exact numbers shown in this manuscript were extracted from first simulated data, and a 2.5-97.5 percentile range assessed from all the simulations is presented with all the results.

All statistical analyses were performed using R software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics (version 27; IBM Corp, Armonk, NY).

RESULTS

Patient characteristics are presented in Table 1. The median follow-up duration was 5.8 years (range, 0-19 years). Altogether, 697 (94%) patients received first-line, 231 (31%) second-line, and 72 (10%) third-line treatments (Fig 1). Given treatments in different therapy lines are presented in Table 2. The median PFS after each line was 8.1 years (95% CI, 7.0 to 9.3), 4.2 years (95% CI, 2.8 to 5.6), and 2.2 years (95% CI, 1.7 to 2.8). The 5-year PFS after each line was 62%, 47%, and 32%, respectively.

In simulated data, 96% (2.5-97.5 percentile range in 1,000 simulations: 95%-96%) of the patients had received first-line, 38% (38%-44%) second-line, 15% (14%-18%) third-line, and 4% (3%-6%) fourth-line therapies within 10 years of diagnosis. By 20 years, the numbers were 97% (96%-98%), 66% (61%-70%), 34% (30%-41%), and 15% (9%-18%). The

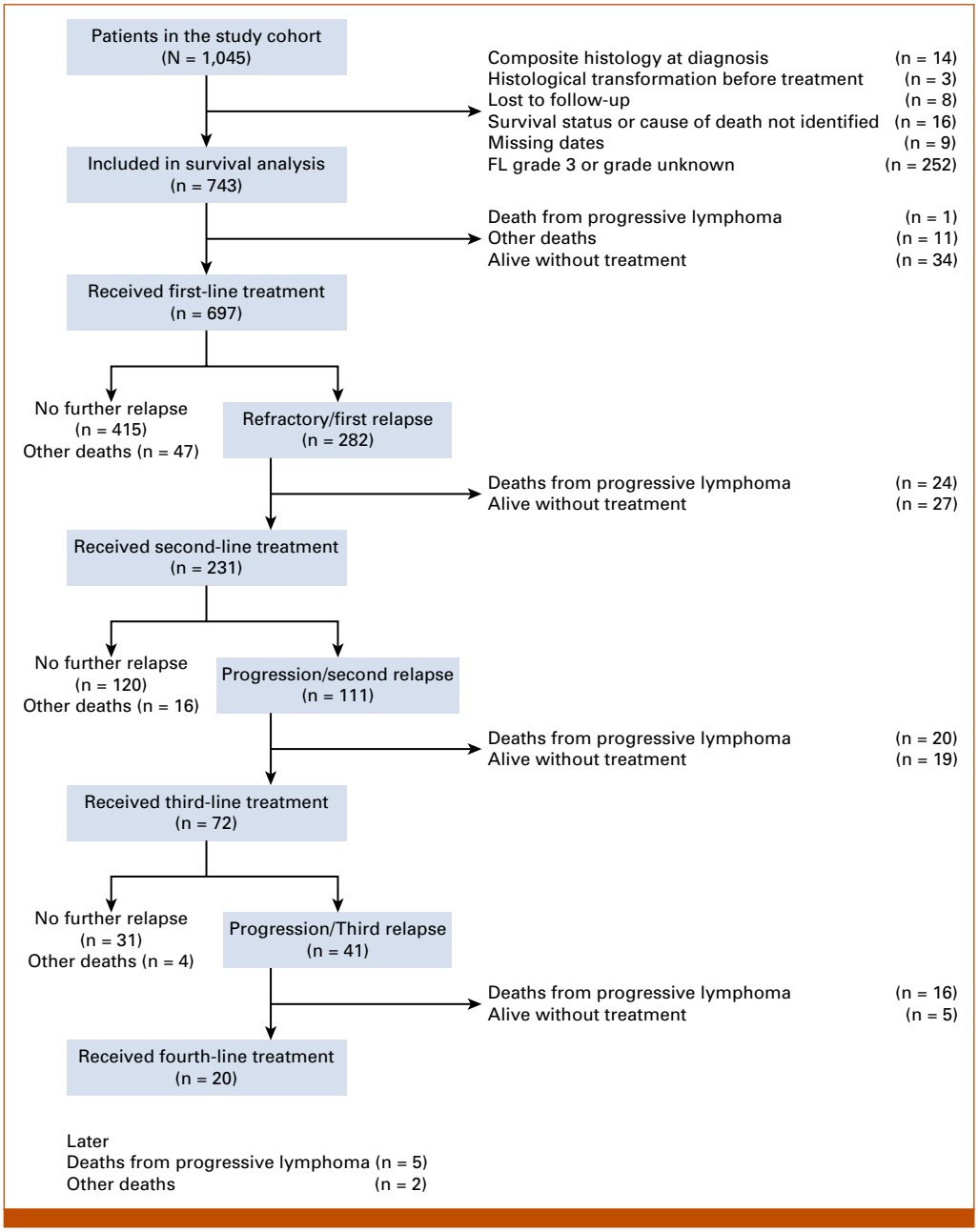

FIG 1. Flow chart explaining eligibility and inclusion for the study population. FL, follicular lymphoma.

median number of therapy lines received was one in 10 years and two in 20 years (Table 3).

The median overall survival in the simulated data was 15 years (2.5-97.5 percentile range, 14-15 years). The state distribution plot of the simulated data (Fig 2) shows that within 10 years of diagnosis, 30% (29%-34%) of the patients had died, approximately half of them from progressive lymphoma (47% [43%-53%]). Of the living patients, 3% (2%-4%) had not required any active treatment for 10 years, whereas 61% (54%-61%) had received one line, 25% (23%-30%) two lines, 8% (7%-12%) three lines, and 3% (2%-5%) four or more lines of therapy.

Within 20 years of diagnosis, 70% (69%-78%) of the patients had died, and both causes of death were still approximately equally common (deaths from progressive lymphoma: 52% [43%-58%]). Of the living patients, only 1% (0%-2%) did not require any active treatment, whereas 28% (15%-32%) had received one, 48% (34%-54%) two, 15% (15%-33%) three, and 9% (4%-15%) four or more lines of therapy.

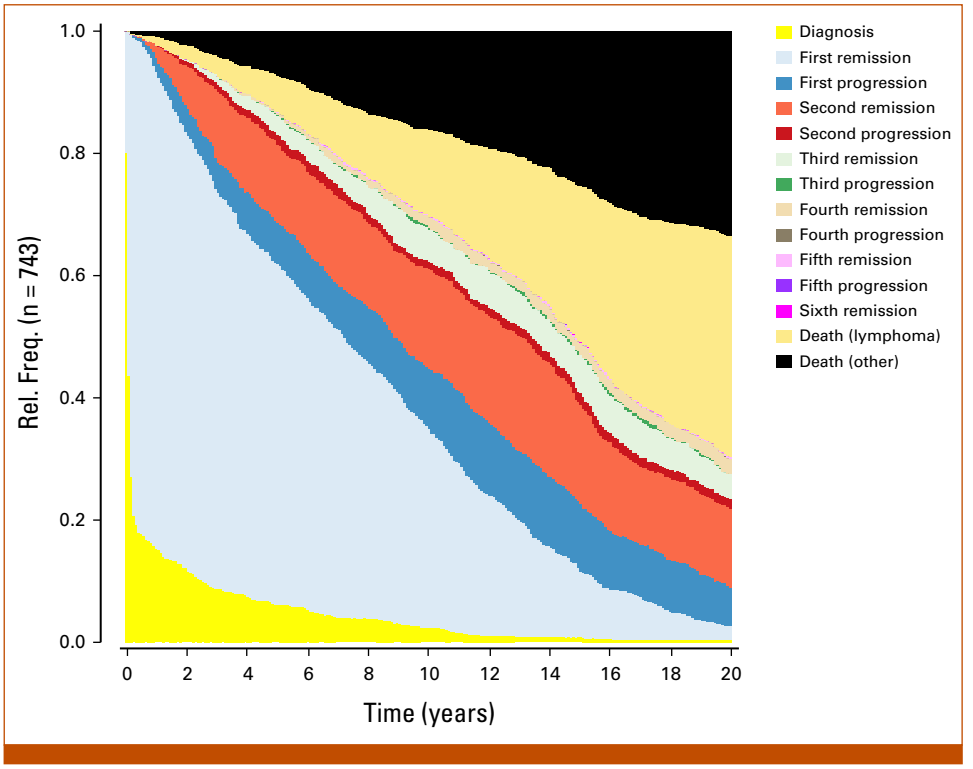

FIG 2. A simulated state distribution plot of 743 patients with low-grade FL. The simulation was carried out by a competing risk model on the basis of Weibull distribution and afterward the data were completed by imputing. FL, follicular lymphoma; Rel. Freq., relapse frequency.

DISCUSSION

In this study, we simulated the lifetime treatment burden of patients with low-grade FL. In our analysis, nearly all patients (97%) received at least one active therapy during the disease period. Meanwhile, approximately two third of the patients received at least two lines and one-third at least three lines of therapy.

Estimates of the proportion of patients who receive subsequent therapy lines are of great value when introducing novel therapies with increased societal cost. Such therapies, including inhibitors of phosphatidylinositol 3-kinase[5] and enhancer of zeste homolog 2,[6] anti-CD20/CD3 bispecific antibodies,[2] and CAR T-cell therapies,[1,7] are studied in patients with relapsed or refractory FL in third or later lines. However, there is a lack of knowledge regarding the number of patients eventually proceeding to third-line treatment and possibly needing these therapies. The fact that one-third of the patients would be third-line therapy candidates will help in carrying out reliable health economic calculations. Our analysis demonstrates that shifting a new type of therapy from fourth to third line will triple the number of candidates for the therapy and simultaneously increase the treatment costs. Yet, if the therapy in question proves to be more efficient in earlier lines, it might reduce the number of patients needing further treatments. To be able to address these benefits of novel therapies, it is important to know the lifetime treatment burden with current practices.

In an observational National LymphoCare Study with 2,652 patients and a 8-year follow-up, 92% (n = 2,429) of the patients received first-line, 34% second-line, 17% third-line, and 9% fourth-line therapies.[3] Similarly, Batlevi et al[4] reported that after a follow-up of 8.3 years, of 1,088 patients, 85% received first-line, 42% second-line, 27% third-line, and 18% fourth-line therapies. These reports of real-life nature offer good comparison with our simulation. However, considering the relatively short follow-up in all of these real-life studies, patients with aggressive subtypes and short response durations are probably emphasized. On the basis of our simulation, it seems that patients tend to have relapses beyond 10 years of diagnosis, and the total treatment burden increases further from 10 to 20 years.

The simulation was based on PFS times, which are associated with high inborn heterogeneity. Apart from simple patient- and lymphoma-related factors, length of PFS is also highly dependent on factors such as diagnostic delay, threshold of treatment initiation, treatment intensity, conduct of routine surveillance scans, and possible changes in therapy because of treatment-related toxicities. Interestingly, several studies have shown that longer PFS does not necessarily associate with better OS, although previous

TABLE 1. Patient Characteristics

Variable	N = 743
Age, years, median (range)	60 (18-100)
Sex, No. (%)	
Female	378 (51)
Male	364 (49)
NA	1
Stage, No. (%)	
I-II	241 (34)
III-IV	468 (66)
NA	34
FLIPI, No. (%)	
0-1	244 (37)
2	193 (29)
3-5	229 (34)
NA	77
LDH level, No. (%)	
Normal	415 (73)
Elevated	155 (27)
NA	173
Hb, g/dL, No. (%)	
<12	95 (14)
≥12	588 (86)
NA	60
B-symptoms, No. (%)	
Yes	124 (17)
No	596 (83)
NA	23
Initial treatment,[a] No. (%)	
Immunochemotherapy	493 (71)
Anthracycline-containing regimens	375 (54)
Bendamustine/fludarabine-containing regimens	82 (12)
Maintenance with rituximab after first-line therapy,[a] No. (%)	207 (30)

Abbreviations: B-symptoms, systemic symptoms (unexplained weight loss, fever, night sweats); FLIPI, Follicular Lymphoma International Prognostic Index; Hb, hemoglobin; LDH, lactate dehydrogenase; NA, not available.
[a]Of the patients who received first-line therapy (n = 697).

TABLE 2. First-, Second-, and Third-Line Treatments of the Patients

Factor	First Line	Second-Line	Third-Line
No. of patients who received therapy line, (%)	697 (94)	231 (31)	72 (10)
Immunochemotherapy, No. (%)	493 (71)	130 (56)	44 (61)
Anthracycline-containing regimen	350	47	3
Bendamustine	60	40	15
Fludarabine-containing regimen	10	10	2
Platinum-based regimen	—	4	9
Less-intensive therapies	58	22	10
Others	15	7	5
Chemotherapy without rituximab, No. (%)	69 (10)	52 (23)	16 (22)
Anthracycline-containing regimen	25	10	—
Bendamustine	1	4	1
Fludarabine-containing regimen	11	17	1
Platinum-based regimen	—	6	—
Less-intensive therapies	30	12	4
Others	2	3	10
Rituximab-monotherapy, No. (%)	28 (4)	14 (6)	4 (6)
Radiation therapy only, No. (%)	91 (13)	34 (15)	7 (10)
Surgical removal only, No. (%)	14 (2)	1 (0.4)	—
Missing information of the given therapy, No. (%)	2 (0.3)	—	—
Stem-cell transplantation, No. (%)	44 (6)	31 (13)	7 (10)
Maintenance with rituximab,[a] No. (%)	207 (42)	47 (36)	11 (25)

NOTE. All the percentages are of patients who received an active therapy (number of patients seen in the first row). Less-intensive therapies include cyclophosphamide alone or together with prednisolone and vincristine (C, COP), chlorambucil, and gemcitabine. Other therapies include in first line: radioimmunotherapy (90Y-ibritumomab tiuxetan) and bortezomib; in second line: MINE/MIME (mesna, ifosfamide, mitoxantrone/methothrexate, and etoposide) and heterogeneous chemoregimens; in third line MINE/MIME, radioimmunotherapy, idealisib, copanlisib, bortezomib, ibrutinib, and heterogeneous chemoregimens.
[a]Of the patients who were treated with immunochemotherapy.

studies agree that response duration shorten after each treatment line.[3,4,8] Longer remissions but no OS benefit has been shown when comparing immediate treatment with watchful waiting in asymptomatic patients,[9,10] immunotherapy alone with immunochemotherapy,[11] and rituximab maintenance with observation after frontline immunochemotherapy.[12] Eventually, the number of therapy lines received is highly dependent on the aforementioned facts, and our results represent a real-world setting with variable practices.

Strengths of this study were the inclusion of relatively large number of patients and a multicenter, binational, population-based setting representing both university and central hospitals. To our knowledge, this study is the first to introduce a simulation to describe the lifetime treatment burden of patients with FL. However, this simulation is hypothesis-based and only an estimate as

TABLE 3. Cumulative Incidence of Active Therapy Lines Received by Patients With Low-Grade Follicular Lymphoma in Simulated Data Within 10 and 20 Years of Diagnosis

Therapy line, % of patients (2.5-97.5 percentile range)	10 Years	20 Years
First	96 (95-96)	97 (96-98)
Second	38 (38-44)	66 (61-70)
Third	15 (14-18)	34 (30-41)
Fourth	4 (3-6)	15 (9-18)
Median number of therapy lines received	1	2

real-world data are not available. With all its limitations, we find it the best way to obtain up-to-date estimates of lifetime treatment burden in patients with FL. Similar simulations could be used also among other patient groups, including patients with chronic lymphatic leukemia and other indolent lymphomas; technically in any data set with state transitions, each transition being a competing risk model.

The main limitations include the relatively short median follow-up of the study population on which the simulation was based. However, the follow-up can be read to provide a good balance between long enough follow-up and a treatment paradigm that can still be used to inform present-day patients. Nonetheless, this simulation represents the time period from 1997 to 2016, the majority of the patients having received rituximab but before the introduction of novel therapeutics. Patients diagnosed today might have different prognosis compared with this patient cohort. We suggest, therefore, that this kind of simulations should be repeated on a regular basis, at least after a substantial change in treatment algorithm. In addition, histologic transformations were not systematically documented but they were captured as progressing lymphoma. Therefore, this simulation cannot address the magnitude of the phenomena during patients' lifespan.

In conclusion, this study provides a new tool for clinicians and policymakers to estimate the number of patients receiving subsequent therapy lines and to understand the current status of FL in a rapidly evolving landscape.

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K.S. and O.K. contributed equally to this work.

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DATA SHARING STATEMENT

The datasets generated during the current study are available from the corresponding author for reasonable requests.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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