Second-line and subsequent therapy and outcomes for follicular lymphoma in the United States: data from the observational National LymphoCare Study

Follicular lymphoma (FL) is the second most common lymphoma, and by virtue of its chronicity, may be the most prevalent and most treated lymphoma in the United States (Morton *et al*, 2006). The National LymphoCare Study (NLCS, ClinicalTrials.gov identifier, NCT00097565) is a prospective cohort study of disease presentation, treatment patterns and clinical outcomes that recruited consecutive patients diagnosed with FL between March 2004 and March 2007 in participating sites in the United States. The NLCS prospectively collected quarterly observations regarding disease characteristics, subsequent therapies and observed responses. Patterns of initial management in this cohort were reported previously (Friedberg *et al*, 2009). The current report describes patterns of subsequent active treatment and outcomes.

"First-line treatment" refers to the first *active* treatment (Rx1), and "second-line treatment" refers to the second *active* treatment (Rx2), regardless of whether a relapse was recorded after first treatment. Maintenance therapy was not considered a distinct active treatment.

Time to Rx2 was defined as the number of days from initiation of Rx1 to initiation of Rx2. Response/progression was determined by the local treating investigator. Patients progressing within 24 months of Rx1 were classified as early progressors (Casulo *et al*, 2015). Rituximab-refractory patients were identified from those who received rituximab monotherapy (R-mono) or rituximab plus chemotherapy (R-chemo) with or without rituximab maintenance therapy as Rx1. Patients with progressive disease (PD) within 6 months of completing rituximab-containing Rx1 or following rituximab maintenance therapy were considered rituximab-refractory.

After a median follow-up of 8 years (range: 0·02–10·34), 2429/2652 patients had received Rx1. Of those, 889 (37%) had received Rx2, 438 (18%) had received a third active treatment (Rx3), and 229 (9%) and 123 (5%) had received four and five active treatments, respectively (Fig 1). Overall, 1465 (53%) patients remained in active follow-up at study closure; 23% had died and 24% were lost to follow-up, withdrew or discontinued for other reasons. The distribution of treatment choices for Rx1 to Rx5 is shown in Table I.

The median time from initiation of Rx1 to Rx2 (n = 889) was 16 months (range: 0·1–112). Of patients who received Rx2, 62% did so within the first 24 months (Fig S1). The distribution of treatment choices for Rx1 is notably different than for Rx2, with a substantial increase in the use of R-mono, a mild increase in chemotherapy without rituximab, and a substantial drop in patients receiving chemoimmunotherapy for Rx2 compared with Rx1. Rituximab remained a treatment component (alone or with chemotherapy) in 70% of patients receiving Rx2.

Of the patients receiving R-mono for Rx1, 44% continued to use R-mono for Rx2, while 34% switched to R-chemo. Of the patients receiving R-chemo for Rx1, 41% also used R-chemo for Rx2, 26% switched to R-mono and 33% to other therapy. The rate of anthracycline use was only 18% for Rx2, and 28% of patients remained anthracycline-naïve after five active treatments. Bendamustine was unavailable in the United States during the time of patient enrolment and was used in 9/2429 patients for Rx1, 50/889 for Rx2 and 56/438 for Rx3. The participation rate in a clinical trial for Rx2 remained low at 5%; 22% of patients who participated in a clinical trial for Rx2 had also participated in a clinical trial for Rx1.

Overall, 341 patients were classified as early progressors. The distribution of Rx2 choices was notably similar between early progressors and others who received Rx2, with early progressors only slightly less likely to receive R-mono (30% vs. 36%) or investigational therapy (4·4% vs. 6·5%), and slightly more likely to receive any anthracycline (18% vs. 13%) or radioimmunotherapy (6·8% vs. 4·0%). Remarkably, although more frequently than others (1·1%), only 3·5% of early progressors received Rx2 strategies that included bone marrow transplant (BMT). Among patients who had received ≥5 treatments, use of radioimmunotherapy in the relapse/progression setting (n = 77) outpaced BMT (n = 53).

Of 237 rituximab-refractory patients who received Rx2, 77 and 160 had received Rx1 of R-mono (217 rituximab-refractory patients) and R-chemo (486 rituximab-refractory patients), respectively. Among rituximab-refractory patients, 62% received rituximab-containing Rx2, including 22% who received R-mono; compared with 36% of patients receiving R-mono in the non-refractory cohort. Other Rx2 choices among rituximab-refractory patients included chemotherapy alone (13%), radioimmunotherapy (9%), radiation therapy (7%) and BMT (5%).

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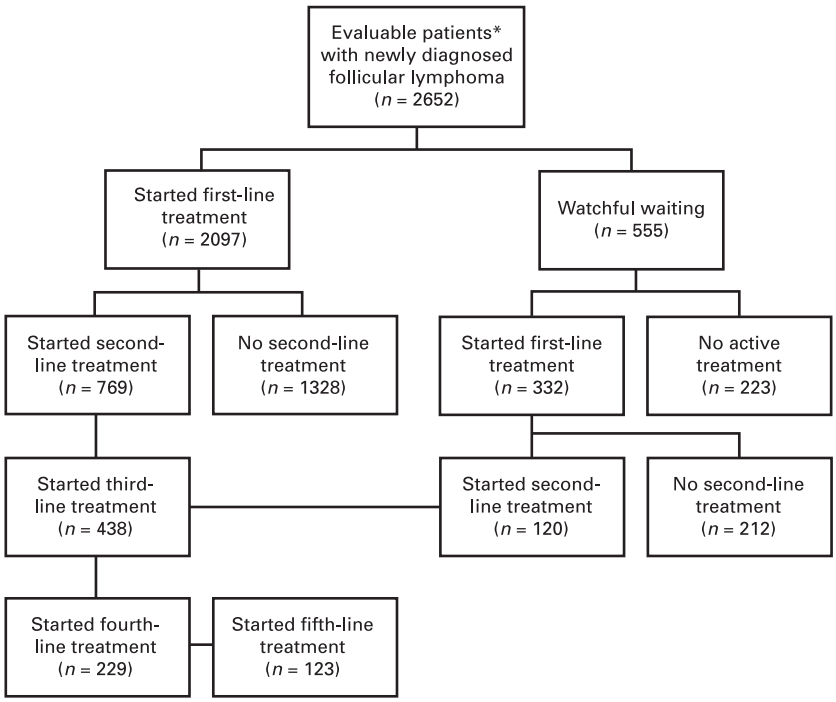

Fig 1. Distribution of treatment frequencies. *Patients with mixed histology or other lymphoma or found ineligible after enrolment were excluded. Patients who experienced a progression event prior to the beginning of the first assigned treatment strategy were also excluded.

Table I. Distribution of first-line to fifth-line treatment.

Treatment	Rx1 (n = 2429)	Rx2 (n = 889)	Rx3 (n = 438)	Rx4 (n = 229)	Rx5 (n = 121)
Rituximab	457 (19%)	279 (31%)	98 (22%)	35 (14%)	18 (15%)
R-chemo	1413 (58%)	345 (39%)	170 (39%)	79 (35%)	44 (36%)
Rituximab + anthracycline	828 (34%)	111 (12%)	51 (12%)	12 (5%)	8 (7%)
Rituximab + alkylator	424 (17%)	180 (20%)	89 (20%)	50 (22%)	25 (21%)
Rituximab + fludarabine	142 (6%)	43 (5%)	26 (6%)	11 (5%)	5 (4%)
Other R-chemo	19 (1%)	11 (1%)	4 (1%)	6 (3%)	6 (5%)
Chemotherapy	85 (3%)	77 (9%)	59 (13%)	37 (15%)	24 (20%)
BMT	6 (<1%)	17 (2%)	13 (3%)	17 (7%)	10 (8%)
Radiation (XRT)	261 (11%)	31 (7%)	31 (7%)	23 (10%)	15 (12%)
Radioimmunotherapy	10 (<1%)	45 (5%)	26 (6%)	11 (5%)	2 (2%)
Investigational	183 (8%)	45 (5%)	34 (8%)	21 (9%)	7 (6%)
Other therapies	14 (1%)	16 (2%)	7 (3%)	6 (5%)	1 (1%)

BMT, bone marrow transplant; R-chemo, rituximab plus chemotherapy; Rx, active treatment line; XRT, external beam radiation therapy.

PFS (Figs S2 and S3, Tables SI and SII) was longest following Rx1 (median: 6·6 years) and was diminished following Rx2 (median 1·5 years) and again following Rx3, Rx4 and Rx5 (median: 0·83, 0·69 and 0·68 years, respectively). PFS following Rx2 was remarkably similar for R-mono (median: 1·5 years; 45% at 2 years, 28% at 5 years) and R-chemo (median: 1·5 years; 42% at 2 years, 28% at 5 years). The observed overall response rate (ORR) following R-mono as Rx2 was 55% overall, 43% (95% confidence interval [CI]; 29–58) for rituximab-refractory patients and 59% (95% CI; 51–67) for non-rituximab-refractory patients. PFS also differed with medians of 0·47 years (95% CI; 0·25–1·31) and 1·58 years (95% CI; 1·19–2·95) for rituximab-refractory and non-rituximab-refractory patients, respectively. Median overall survival was 5·52 years for rituximab-refractory patients, while it was not reached for non-rituximab-refractory patients.

Several notable observations from this description emerge, including: the relatively low fraction of patients receiving multiple therapies during the first several years of management; the frequent utilization of rituximab in second and subsequent treatments, somewhat irrespective of refractoriness to rituximab-based therapy; the relative avoidance of anthracycline use; the paucity of stem cell

transplant utilization, even among early progressors; and the very low participation rate in clinical trials among FL patients. Referrals for early progressors need to increase for clinical trials such as the National Clinical Trials Network intergroup study S1608, which is focusing on this vulnerable population (NCT03269669).

These data give some clarity to the characteristics of patients who are treated in the relapsed/refractory setting of FL, and serve as a benchmark to evaluate the impact of the integration of novel agents, as well as identify patient and provider preferences for a "standard of care" or control group, in clinical trial development.

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Role of the funder/sponsor

The funder was involved in conception and design of the study, data analysis and interpretation, manuscript preparation, and approval for submission.

Author contributions

BKL, JRC, BD, ADZ, CRF, JWF and KLD: conception and design of the study. BD, ADZ, JWF and CRF: collection and assembly of data. BKL, JRC, BD, ADZ, CRF, JWF and XZ: data analysis and interpretation. BKL, BD, XZ, ADZ, KLD, JRC, CRF and JWF: writing of the manuscript and approval of the final version.

Conflict of interest disclosures

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Fig S1. Cumulative number of patients receiving second-line treatment by time from initiation of first-line treatment.

Fig S2. Kaplan–Meier survival curves for progression-free survival (from start of first-line to fifth-line treatments), by treatment line. PFS, progression-free survival.

Fig S3. Kaplan–Meier survival curves for progression-free survival (from start of second-line treatment), among patients receiving second-line R-mono, by rituximab-refractoriness. PFS, progression-free survival; R-mono, rituximab monotherapy; R-refractory, rituximab-refractory.

Table SI. Progression-free survival from start of first-line to fifth-line treatments, by treatment line.

Table SII. Progression-free survival and overall survival from start of second-line treatment, among patients receiving second-line R-mono or R-chemo, by second-line treatment and by rituximab-refractoriness for R-mono patients.

References

Casulo, C., Byrtek, M., Dawson, K.L., Zhou, X., Farber, C.M., Flowers, C.R., Hainsworth, J.D., Maurer, M.J., Cerhan, J.R., Link, B.K., Zelenetz, A.D. & Friedberg, J.W. (2015) 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. *Journal of Clinical Oncology*, **33**, 2516–2522.

Friedberg, J.W., Taylor, M.D., Cerhan, J.R., Flowers, C.R., Dillon, H., Farber, C.M., Rogers, E.S., Hainsworth, J.D., Wong, E.K., Vose, J.M., Zelenetz, A.D. & Link, B.K. (2009) Follicular lymphoma in the United States: first report of the National LymphoCare Study. *Journal of Clinical Oncology*, **27**, 1202–1208.

Morton, L.M., Wang, S.S., Devesa, S.S., Hartge, P., Weisenburger, D.D. & Linet, M.S. (2006) Lymphoma incidence patterns by WHO subtype in the United States, 1992–2001. *Blood*, **107**, 265–276.