Annals of Hematology (2019) 98:175–183
https://doi.org/10.1007/s00277-018-3501-8

ORIGINAL ARTICLE

Burden of illness of follicular lymphoma and marginal zone lymphoma

Neerav Monga[1] · Loretta Nastoupil[2] · Jamie Garside[3] · Joan Quigley[4] · Moira Hudson[4] · Peter O'Donovan[4] · Lori Parisi[5] · Christoph Tapprich[1] · Catherine Thieblemont[6,7,8]

Received: 17 September 2018 / Accepted: 17 September 2018 / Published online: 13 October 2018

Abstract

Follicular lymphoma (FL) and marginal zone lymphoma (MZL) are two subtypes of indolent B cell non-Hodgkin lymphoma (NHL) that account for approximately 20% and 12% of all NHLs, respectively. FL and MZL are rare conditions with orphan disease designations. We conducted a comprehensive review of the burden of FL and MZL that encompasses the epidemiological, real world clinical, economic, and humanistic impact of these diseases globally. A targeted literature search identified 31 eligible studies for review. Epidemiological coverage was poor, with data obtained for studies from only seven countries. The incidences of both subtypes were low: age-standardized incidence rates of FL ranged from 2.1/100,000 in France to 4.3/100,000 in the USA, while for MZL it varied geographically from 0.5/100,000 in Australia to 2.6/100,000 in the UK. The cumulative total direct healthcare costs for FL were higher for patients with progressive disease compared to those without ($30,890 vs. $8704 at 12 months, respectively) and main driver of costs related to the use of chemotherapy. Five-year overall survival was improved in patients with FL compared with MZL (e.g., 76.5% vs 60.7% in one study that reported on both subtypes). Mortality rates were particularly lower in female patients with FL aged < 60 years. However, limited outcome data for MZL patients were identified. FL and MZL contribute significant burden on healthcare systems and on patients globally, with delays in progression potentially leading to cost savings. More rigorous characterization of these two NHL subtypes, new and more effective treatments, and standardization of reporting would lead to a more robust understanding of future data in this disease area.

Keywords MZL · FL · Epidemiology · Costs · Economics · QoL

Introduction

Follicular lymphoma (FL) and marginal zone lymphoma (MZL) are two subtypes of indolent B cell non-Hodgkin lymphoma (NHL) that account for approximately 20% (FL) and 12% (MZL) of all NHL [1]. Both subtypes have orphan drug designations. FL affects approximately 3.7 in 10,000 individuals in the European Union (EU), which is below the EU threshold for orphan designation of 5 in 10,000 individuals [2].

A number of guidelines are available to inform treatment and management decisions for patients with NHL subtypes at different disease stages [3–8]. Although guidance on treatment is available, the global burden of disease for FL and MZL remains unclear. Therefore, we sought to evaluate the real-world burden of disease for these two NHL subtypes and to identify key data gaps in the G20 countries to determine opportunities for future research by conducting four targeted literature reviews of: (i) epidemiological data; (ii) overall economic burden of disease; (iii) clinical burden; and (iv) humanistic burden.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00277-018-3501-8) contains supplementary material, which is available to authorized users.

✉ Neerav Monga
nmonga@ITS.JNJ.com

1 Janssen Oncology, Toronto, ON, Canada
2 Department of Lymphoma/Myeloma, The University of MD Anderson Cancer Center, Houston, TX 77030, USA
3 Janssen EMEA HEMAR, High Wycombe, London, UK
4 ICON Health Economics and Epidemiology, Boston, USA
5 Medical Affairs, Janssen, Raritan, NJ, USA
6 APHP, Hemato-Oncology, Hôpital Saint-Louis, Paris, France
7 Sorbonne Paris-Cité, Diderot University, EA3788 Paris, France
8 Descartes University, Paris, France

Methods

Searches were run from January 2006 to November 2016 in the following electronic databases: MEDLINE®, MEDLINE in-process; E-pubs ahead of print (Ovid SP®), Embase (Ovid SP), National Health Services Economic Evaluation Database (NHS EED; not for epidemiology), and EconLit (not for epidemiology). Eligibility criteria for the four reviews are shown in Suppl. Table 1. Search strategies included free text and controlled vocabulary terms (Medical Subject Headings in MEDLINE and Emtree terms in Embase) for the population and outcomes of interest. Three search strategies were developed to capture (i) epidemiological data, (ii) economic and clinical burden data; and (iii) humanistic burden data. Details of the search strategies used are provided in Suppl. Table 2. As these targeted literature reviews focused on real-world evidence, randomized clinical trials were not included. Abstracts and full publications were reviewed independently by two reviewers, with adjudication by a third reviewer as required. A PRISMA flow diagram showing the numbers of studies included and excluded at each stage of each review is provided in Suppl. Fig. 1 [9].

The following data were extracted for each of the four reviews: (i) epidemiology review (incidence, prevalence); (ii) economic burden review (time horizon, analysis perspective, currency, total direct medical costs and component costs, total direct nonmedical costs and component costs, indirect costs, resource use); and (iii) clinical burden review (long-term outcomes/prognosis, mortality rates); (iv) humanistic burden (caregiver burden, impact on family, generic QoL, and mean change from baseline score in QoL measurements). All available data were extracted into a bespoke extraction sheet in Microsoft Excel® and journal websites for included articles were checked for supplementary data and errata. Data were verified by a second reviewer.

Results

Epidemiology

Of the 468 references retrieved by the epidemiology search (Suppl. Table 2), 11 studies were eligible for inclusion following abstract and full text review [10–20]. Of these, the majority (6/11) were from the USA, and five studies each reported data from the UK, France, Italy, the Netherlands, Japan, and Australia. There were limited or no data for many G20 countries. All studies reported data from national cancer registries. Full details of the studies are included in Suppl. Table 3A.

The overall incidence of both FL and MZL is low, consistent with their orphan disease designation: the age-standardized incidence (per 100,000) for FL ranged geographically from 2.1 in France [14] to 4.3 in the USA [11], whereas that of MZL was lower at 0.5 in Australia [20] to 2.62 in the UK [18]. All studies reporting data for both NHL subtypes followed this trend, except Smith et al. 2015 who reported the incidence (per 100,000) of FL and MZL to be approximately equivalent in the UK at 2.81 and 2.62 FL and MZL, respectively [18]. For full details of the epidemiological data extracted see Suppl. Table 3A and Table 4 for point estimates.

Incidence of FL and MZL disaggregated by sex was reported by two studies (Suppl. Table 4). Chihara et al. 2014 [10] found that for the years 2006–2008, the incidence of both FL and MZL was higher in males than in females. While Smith et al. 2015 [18] also reported a higher incidence of MZL in males than in females, the incidence FL was, conversely, marginally lower in males than females.

The most comprehensive data for the incidence of MZL subtypes was that of Olszewski 2013 [17] who reported that extranodal MZL is the most common subtype.

Only one study reported prevalence of FL and MZL at 3, 5, and 10 years (Fig. 1) [18]. The overall 10-year prevalence of FL was 25.2/100,000 population, with a higher prevalence in females than males (prevalence 26.2 vs. 24.1/100,000, respectively). Overall 10-year prevalence of MZL was lower than FL at 23.8/100,000 population, with a higher prevalence in males than females (prevalence 26.7 vs. 21.1/100,000, respectively).

Economic burden

Of the 1208 references retrieved by the combined clinical and economic burden search (Suppl. Table 2B), four studies (three from the USA, one from Denmark) were eligible for inclusion following abstract and full-text review [21, 29–31]. All studies reported data for FL; no economic data for MZL were identified. Full details of the studies are shown in Suppl. Table 3B.

Direct cost data for FL were reported by the three US studies [21, 29, 30]. Danese et al. 2016 reported the mean incremental cost difference for chemotherapy+rituximab vs. chemotherapy alone in males and females to be the same ($28,211) [29].

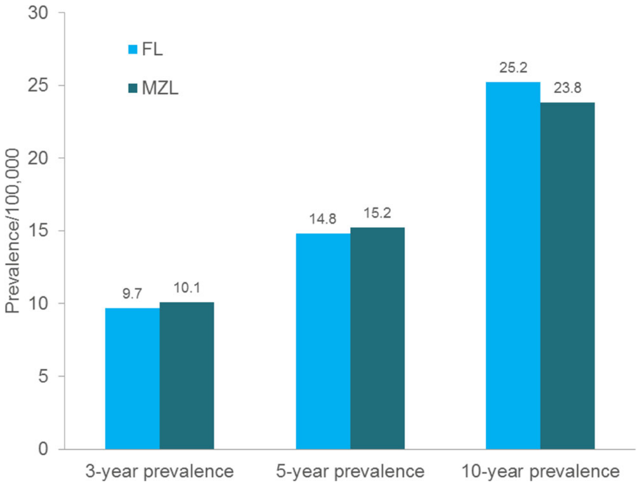

Fig. 1 Epidemiology of FL and MZL: UK 3-, 5-, and 10-year prevalence for all FL and MZL patients (UK data; Smith 2015)

Griffiths et al. 2012 reported a mean cost of $15,640 for rituximab, and average cost per administration of $2836. In Beveridge 2011, the main driver of overall cost appeared to be the cost of pharmaceuticals, specifically rituximab plus chemotherapy (Table 1) [21]. The 12-month cumulative costs for patients with progressive disease (PD) were approximately 3.5 times those for patients with non-PD ($30,890 vs. $8704) [21]. Analysis of the 6-month mean costs per patient per year shows that chemotherapy, acute and outpatient visits, and laboratory procedures were notably higher in patients with PD [21]. None of the three studies reported indirect costs.

Data on resource use were reported in one US study [21]. Beveridge et al. 2011 [21] found that patients with PD attended four times more chemotherapy visits per month than those with non-PD (mean chemotherapy visits/patient/month 0.88 vs. 0.17, respectively). Likewise, progressive FL was associated with more outpatient visits (3×) and laboratory procedures (2.2×), whereas the two categories of patients experienced the same median number of acute care visits monthly (0.66) [21].

Horsboel et al. 2013 [31] reported that 28% of patients in a Danish registry were unable to return to work after taking sick leave due to FL. Further, at 3 years post-diagnosis, 34% of patients who had taken long-term sick leave were still unable to return to work [31].

Real-world clinical burden

Among the 1208 references retrieved by the combined clinical and economic burden search (Suppl. Table 2B), 24 studies were eligible for inclusion [11, 13, 15, 17, 18, 22–29, 32–42]. All were nonrandomized retrospective observational studies, reporting clinical burden in FL/MZL across ten countries (mostly the USA; 11/24; full details of the studies are provided in Suppl. Table 3C).

Nineteen studies reported survival data. The most commonly reported survival metric was 5-year OS.

The 5- and 10-year OS ranges for patients with FL or MZL, in studies that stratified survival data by one or more categories (age, sex, treatment regimen), are shown according to treatment status at study entry and reporting category in Table 2 and Table 3, respectively.

Follicular lymphoma

As expected, OS was higher in younger than in older patients [27]. However, the survival rates reported by Conconi et al. 2015 suggest that, from 1985 onwards, outcomes have improved substantially over time (< 40 years 81%; 41–59 years 68%; > 60 years 32%) [22]. This is supported by similar conclusions drawn by Prochazka et al. 2017 [26].

Another potential modifier of survival may be patient sex. Nabhan et al. 2016 [36] found a notable difference in survival between male and female patients with FL > 80 years old (HR 0.50; 95% CI 0.31–0.82); suggesting poorer survival in males. However, differences in sex were not observed across all age groups, (such as patients who were 51–60 years old) [36]. Conversely, Smith et al. 2015 reported a 5-year survival data stratified by sex and found

Table 1 Direct costs associated with FL in treatment-experienced patients with and without disease progression

Patient subgroup		Direct drug costs ($US)		Direct non-drug costs ($US)	
	Overall cost ($US)	Component	Cost	Component	Cost
Without disease progression					
6-month mean per patient per month	859.98	Chemotherapy infusion	655.75	Outpatient visits	36.68
		R monotherapy	487.07	Acute care	2.46
		R chemotherapy	166.07	Laboratory costs	11.35
		Other chemotherapy	2.61	Minor procedures	2.79
		Other medication	101.86	Other	0.59
				External radiation treatment	15.07
				Other radiotherapy	32.59
With disease progression					
6-Month mean per patient per month	3527.4	Chemotherapy infusion	2495.01	Outpatient visits	99.92
		R monotherapy	849.5	Acute care	24.14
		R chemotherapy	1610.86	Laboratory costs	28.53
		Other chemotherapy	34.65	Minor procedures	8.79
		Other medication	700.28	Other	3.02
				External radiation treatment	71.27
				Other radiotherapy	95.41

Abbreviations: *R* rituximab. US data from Beveridge 2011 [21]

Table 2 Summary of 5- and 10-year overall survival data patients with FL according to treatment status at study entry

	Study characteristics	Reporting category	N	5-Year OS [% (range)]	10-Year OS [% (range)]
Treatment naïve at study entry					
Conconi et al. 2015 [22]	Italy, Spain, Switzerland, UK, 1985–2010, retrospective observational	> 60 years	424	–	32 (27–38)*
		41–59 years	426	–	68 (62–73)*
		≤ 40 years	152	–	81 (73–87)*
Gangatharan et al. 2015 [23]	Canada, 1995–2010, retrospective cohort	40–65 years	366	–	72 (NR)
		< 40 years	61	–	87 (NR)
Hirayama et al. 2014 [24]	Japan, 2001–2013, retrospective observational	65–80 years	95	84.4 (NR)	–
		50–64 years	240	93.5 (NR)	–
		20–49 years	108	91.3 (NR)	–
		Stage III	186	89.9 (NR)	–
		Stage IV	257	91.8 (NR)	–
Nabhan et al. 2015 [25]	USA, 2004–2007, cohort	> 80 years	209	58.5 (51.0, 65.3)*	–
		> 80 years, on chemo-immunotherapy	NR	48.9 (35.6, 60.9)*	–
		≤ 60 years	1255	92.2 (90.5, 93.6)*	–
		≤ 60 years, on chemo-immunotherapy	NR	91.2 (88.6, 93.2)*	–
Prochazka et al. 2017 [26]	Czech Republic, 2001–2012, matched pairs analysis	All patients on R-SQ	48	100 (NR)*	–
		All patients on R-CHOP	144	92.1 (0.88–0.97)*	–
Pulte et al. 2012 [27]	USA, 2003–2007, all patients received R-CHOP during study, cohort and model-based projection	≥ 80 years	NR	75.6 (NR)	45.1 (NR)
		75–79 years	NR	77.4 (NR)	56.6 (NR)
		70–74 years	NR	79.9 (NR)	67.7 (NR)
		65–69 years	NR	89.6 (NR)	75.3 (NR)
		60–64 years	NR	87 (NR)	76.3 (NR)
		≥ 60 years	NR	82.1 (NR)	67.2 (NR)
Smith et al. 2015 [18]	UK, 2004–2014, cohort	Male	412	76.5 (71.6–80.7)*	–
		Female	511	74.9 (70.5–78.8)*	–
Treatment experienced/naïve or treatment status unclear at study entry					
Chouhan et al. 2016 [11]	USA, 1973–2012, retrospective observational	≥ 66 years	547	59.9 (55.6–64.0)*	39.1 (34.0–44.0)*
		51–65 years	394	86.7 (82.9–89.8)*	68.8 (62.6–74.2)*
		20–50 years	168	90.9 (85.1–94.6)*	82.0 (73.7–87.9)*
		Stage I	358	79.0 (74.2–83.0)*	57.8 (49.6–65.1)*
		Stage II	200	79.8 (73.3–84.9)*	69.5 (60.7–76.7)*
		Stage III/IV	167	68.2 (60.3–74.9)*	54.4 (43.8–63.8)*
		Stage unknown	384	69.2 (64.3–73.6)*	51.0 (45.8–56.0)*

NR not reported, *R-SQ* rituximab sequential chemotherapy

*95% CI reported

that there was no notable difference between males and females (males, 76.5%; females, 74.9%) [18].

Five- and 10-year survival data for patients who were treatment-experienced, or whose previous treatment status was unknown at study entry were reported by one study (Chouhan et al. 2016) [11] and included the earliest such data reported (1973–2010). As expected, survival outcomes were poorer in this study than in those with a more recent starting point with 10-year survival being only 39.1% in patients ≥ 66 years (1973–2010) and 73.2% in patients > 60 years (2008–2012).

Two studies stratified FL survival data according to disease stage (Table 2). Hirayama et al. 2014 [24] found that 5-year OS in patients with stage III and IV FL were similar (stage III, 89.9%, stage IV, 91.8%) but did not report on patients with stage I/II FL. Chouhan et al. 2016 [11] found that patients with gastrointestinal FL at earlier disease stages had better survival prospects than those with later stage disease (stage I, 79.0%; stage II, 79.8%; stage III, 68.2%; stage IV, 69.2%). However, the significance of these differences is undetermined as the ranges overlap substantially and *p* values were not calculated.

Table 3 Summary of 5- and 10-year overall survival data patients with MZL according to treatment status at study entry

	Study characteristics	Reporting category	*N*	5-Year OS [% (range)]	10-Year OS [% [range)]
Treatment naïve at study entry					
Kuper-Hommel et al. 2013 [13]	Netherlands, 1994–2010, cohort	Nodal > 60 years	NR	62 (NR)	
		Nodal 16–60 years	NR	93 (NR)	
		Extranodal > 60 years	NR	67 (NR)	
		Extranodal 16–60 years	NR	93 (NR)	
Lenglet et al. 2014 [28]	France, 1997–2012, retrospective cohort	Splenic > 60 years	NR	77 (NR)	
		Splenic < 60 years	NR	94 (NR)	
Treatment experience unclear at study entry					
Olszewski et al. 2013 [17]	USA, 1995–2009, cohort	Splenic	1298	67.9 (64.7–70.9)	41.9 (34.6–49.0)
		Nodal	4724	64.2 (62.5–65.8)	44.3 (41.7–46.9)
		MALT	9886	75.4 (74.3–76.3)	58.0 (56.4–59.6)
Smith et al. 2015 [18]		All, male	537	60.7 (55.9–65.1)*	
		All, female	446	61.9 (56.6–66.7)*	
		Systemic[a], male	434	58.3 (52.9–63.3)*	
		Systemic[a], female	338	56.3 (50.0–62.1)*	
		Extranodal, male	103	70.3 (59.6–78.7)*	
		Extranodal, female	108	78.8 (69.2–85.8)*	

NR not reported

*95% CI reported

[a] Smith et al. 2015 [18] used the term systemic MZL, but without assigning an ICD-O-3 code.

Two studies reported 5-year net survival (defined as the measure of excess cancer related mortality compared with the general population matched by age, sex, race, and calendar year) for patients with FL (Migdady 2016, 81.9%; Monnereau 2012, 70%) [33, 34]. Van de Schans et al. 2014 [42] reported conditional 5- and 10-year survival (5-year relative survival rates computed for every additional year of survival up to 15 years after diagnosis, conditional on being alive at the beginning of that year) for both FL and MZL patients (FL 5-year survival rate 79%; 10-year survival rate 86%; MZL 5-year survival rate 90%; 10-year survival rate 93%).

Mortality rates in FL were reported by seven studies with variable follow-up periods. It is clear that mortality is affected by age at diagnosis: for treatment-naïve patients, mortality was 5.44% in patients ≤ 60 years old, and 25.2% in those > 80 years old [36]. Stage of disease also affected mortality rate: patients diagnosed with stage I/II FL between 1995 and 2010 had a mortality rate of 21% compared with 28% for those diagnosed at stage III/IV [35].

Marginal zone lymphoma

Four studies in MZL reported a 5-year survival data according to subtype of MZL [13, 17, 18, 28] (Table 3). One of these also reported a 10-year survival data [17] and two additionally stratified the data according to patient age [13, 28].

Again, as expected, younger patients had better survival outcomes than older patients; for example, for patients who were treatment naïve at study entry and < 60 years vs. > 60 years old, 5-year survival was 93% vs. 62% for nodal MZL, 93% vs. 67% for extranodal MZL, and 94% vs. 77% for splenic MZL, respectively (Table 3) [13, 28]. Two studies analyzed 5-year survival in patients with unclear treatment experience prior to study entry. Olszewski et al. 2013 [17] found that of the three MZL subtypes that examined extranodal MZL had the highest 5- and 10-year OS rates. Olszewski et al. 2013 reported both 5- and 10-year OS data and found that 10-year OS is poorer than 5-year OS, suggesting roughly a 20% decrease in survival. This highlights that although MZL is indolent in nature, it is a life threatening disease [17].

Smith et al. 2015 [18] analyzed data according to patient sex and found that male and female patients with systemic MZL had similar 5-year survival rates (58.3 and 56.3%, respectively). However, male patients with extranodal MZL had poorer survival outcomes than their female counterparts (70.3% vs. 78.8%), the statistical significance of this finding was not reported.

Humanistic burden

Of 252 records retrieved, only three studies (Suppl. Fig. 1C), one each in the UK, the Netherlands, and the USA, reported humanistic burden for FL, and each evaluated QoL using a

Table 4 Evaluation of patients' quality of life according to disease state in FL

Mean values for FACT-Lym domains	Range of scores for each domain	Active disease—newly diagnosed [mean (SD)]	Active disease—relapsed [mean (SD)]	Partial response [mean (SD)]	Remission/complete response [mean (SD)]	Disease free [mean (SD)]	Kruskal-Wallis H test	*p* value
FACT-Lym total	0–168	136.04 (23.22)	109.7 (34.90)	128.81 (24.16)	133.28 (23.71)	135.26 (21.10)	18.79	0.001
Anxiety scale (HADS)	0–21	4.84 (4.56)	7.03 (4.96)	5.52 (3.25)	6.34 (3.99)	3.78 (3.27)	14.42	0.006
Depression scale (HADS)	0–21	3.06 (3.53)	6.09 (3.95)	3.84 (2.55)	3.54 (3.24)	2.30 (2.45)	23.80	< 0.001
WPAI-activity impairment due to health	0–100	26.4 (30.56)	46.18 (37.09)	37.00 (30.06)	26.00 (28.22)	14.80 (22.20)	18.91	< 0.001

Pettengell 2008 [43]

FACT-Lym functional assessment of chronic illness therapy—lymphoma, *FWB* functional wellbeing, *HADS* Hospital Anxiety and Depression Scale, *PWB* physical wellbeing, *SWB* social wellbeing, *WPAI* work productivity and activity impairment

different scale. Pettengell et al. 2008 evaluated QoL by using several scales, data for four of these are shown in Table 4.

Across five FL disease states, there was a clinically meaningful difference (minimal clinical important difference for total FACT-Lym: 6.5–11.2) [44] in QoL between patients with active relapsed disease and those who were newly diagnosed (FACT-Lym total score 109.70 (SD 34.9) vs. 136.04 (SD 23.22); $p = 0.001$ Table 4) [43].

Similarly, patients with active relapsed disease had poorer HADS anxiety and depression scores (7.03 and 6.09, respectively) than patients with active but newly diagnosed disease (4.84 and 3.06, respectively; on a scale of 1–21, where 1 represents no detrimental effect). Work productivity and activity impairment (measured by WPAI) was also examined and found scores of 46.18 and 26.4, respectively, on a scale of 0–100 where 0 represents no detrimental effect), reflecting a greater impairment in work productivity and activity associated with relapsed disease. Pettengel et al. demonstrated that relapsed FL has a significant impact on health-related quality of life across several QoL instruments.

Orlemans et al. 2014 used the EORTC-CLL-16 to evaluate QoL according to treatment type (surveillance; radiotherapy; R-CVP [rituximab, cyclophosphamide, vincristine, prednisone]/rituximab plus chlorambucil; R-CHOP). Newly diagnosed patients treated with chemoimmunotherapy had the lowest health-related QoL due to their more advanced and less localized disease, compared with those either under surveillance or on radiotherapy, respectively [45].

No data were identified for the humanistic burden of MZL.

Discussion

To the best of our knowledge this is the first literature review to summarize the burden of illness in the indolent NHL subtypes FL and MZL. The search strategies used were designed to capture all recent publications addressing the burden of illness across the four domains of epidemiology, economic, clinical, and humanistic burden.

Our findings from the search and analysis of epidemiological data reflect the orphan disease status of both FL and MZL: few studies were identified, and both the incidence and prevalence of the NHL subtypes were very low. Across studies, and in the total population, the incidence of FL was found to be slightly higher than that of MZL. Furthermore, the majority of studies found a higher incidence in males compared with females.

Economic data were identified for FL only, in four studies from two countries (Denmark and the USA). The only available (USA) direct cost data showed the main driver of health care cost was drug costs, and costs were higher for patients who progress compared to those that do not. However, it is worth noting that one-third of patients who go on long-term sick leave cannot return to work because of FL, which imposes additional caregiver and societal burdens.

In the 24 real-world clinical studies included, survival data were reported inconsistently but the most commonly reported outcome was 5-year OS. Comparing such survival data across FL and MZL may necessitate controlling for variables such as age, sex, stage of disease at diagnosis, and treatment regimen during the study. While additional directly comparable data are needed to draw solid conclusions, there are some studies that allow comparison across specific patient groups. One example would be the study by Smith et al. (2015), where male patients with FL had a 76.5% 5-year OS whereas for male patients with MZL this was 60.7% [18].

Within disease subtypes, patient sex was shown to influence OS. Smith et al. 2015 found no difference between males and females for 5-year OS for FL but showed that female patients with extranodal MZL had better survival outcomes than their male counterparts [18]. Nabhan et al. 2016 found a similar difference between male and female patients with FL, with particularly improved mortality rates in females from younger (<

60 years) age groups, suggesting that hormonal effects could play a role in survival [36]. However, the authors stated that further research is required to confirm this as previous studies identified by the authors did not support the role of hormones in the development of lymphoma among postmenopausal women [36].

As expected, patients diagnosed with more advanced FL had poorer survival outcomes than those diagnosed earlier [11, 24], stressing a need for improved early detection, and a need for early treatment. This trend is also observed in patient QoL, as per the findings of the humanistic burden review. Based on the findings, QoL is driven by line and type of treatment received, and patients' response to treatment. Preventing future relapses in FL with effective therapies would have a positive impact on a patient's QoL.

Limitations

Significant data gaps exist for all four aspects of the burden of illness of FL and MZL. Epidemiological, economical, and humanistic data were scarce across the G20 countries. Epidemiological burden data were identified from seven countries, but more than half of these studies were from the USA. No epidemiology data were identified from South America, the Indian subcontinent, Africa, the Middle East, or Russia, and only one study reported data from Asia. Four studies reported economic burden data: one from Denmark and three from the USA. Although treatment of patients with FL and MZL is inevitably a costly process due to the chemotherapies involved, this lack of data across a more diverse cross section of economies is a significant data gap.

Humanistic burden data were only identified in patients with FL. Comparisons across studies were difficult to make due to the inconsistency in tools used to measure QoL with two studies using established measures of QoL (FACT-Lym and the EORTC-CLL-16) while one study used the unestablished PCM. Identification of only three studies for humanistic burden highlights this is also a significant data gap.

Given the large scope of this review, one significant limitation was the non-comparability of study design, and nonstandard use of outcome reporting categories: For example, age group boundaries were not comparable between studies, and studies reported data for disease stage separately or combined. Likewise, treatment modality was diverse, with some studies not reporting on the regimens used. Most importantly, although a small number of studies reported data according to treatment arm, these were too few in number to allow meaningful generalizations to be made about clinical burden with each regimen. The heterogeneity found among these studies further demonstrates the challenges in performing research in orphan diseases. The lack of published data characterizing these two orphan diseases poses challenges to the conduct of clinical trials and the ability to accurately depict meaningful outcomes with novel therapies as illustrated by the slow improvements in survival of FL patients despite more than 40 years of treatment [46].

Conclusions

This comprehensive burden of illness review demonstrates that, for FL/MZL, increased monitoring of the incidence and prevalence, treatment outcomes, and the combined effect of disease and treatment on patient QoL is critical to better characterize these conditions. Further understanding on the economic impact of FL/MZL will help healthcare decision makers determine the impact to health care systems globally and how to best manage the disease from a health care resource perspective.

Based on currently available evidence, FL and MZL contribute to significant burdens on patients globally across many domains. This in turn adds burden to healthcare systems and caregivers, resulting in significant unmet need for more efficacious therapies. Developing new treatments may lead to an improvement in patient QoL and delay increasingly burdensome costs for healthcare providers.

Acknowledgments The authors would like to thank Iain Fotheringham (ICON Plc) and Natalie Nkwor (funded by ICON Plc) for medical writing support in the development of this manuscript.

Compliance with ethical standards

Conflicts of interest Neerav Monga, Jamie Garside, Lori Parisi, and Christoph Tapprich are employees of Janssen.

Loretta Nastoupil and Catherine Thieblemont received research support/honoraria from Janssen.

Joan Quigley, Moira Hudson, and Peter O'Donovan are employees of ICON plc and have received funding from Janssen to conduct/support this research.

References

1. MacDonald D, Prica A, Assouline S, Christofides A, Lawrence T, Sehn LH (2016) Emerging therapies for the treatment of relapsed or refractory follicular lymphoma. Curr Oncol 23(6):407–417. https://doi.org/10.3747/co.23.3405
2. European Medicines Agency (2018) Public summary of opinion on orphan designation: venetoclax for the treatment of mantle cell lymphoma
3. Marcus R, Davies A, Ando K, Klapper W, Opat S, Owen C, Phillips E, Sangha R, Schlag R, Seymour JF, Townsend W, Trneny M, Wenger M, Fingerle-Rowson G, Rufibach K, Moore T, Herold M, Hiddemann W (2017) Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med 377(14):1331–1344. https://doi.org/10.1056/NEJMoa1614598
4. Jacobsen CA, Freedman AS (2012) Early stage follicular lymphoma, current management and controversies. Curr Opin Oncol 24(5): 475–479. https://doi.org/10.1097/CCO.0b013e328356898b
5. Ghielmini M, Vitolo U, Kimby E, Montoto S, Walewski J, Pfreundschuh M, Federico M, Hoskin P, McNamara C, Caligaris-Cappio F, Stilgenbauer S, Marcus R, Trneny M, Dreger P,

Montserrat E, Dreyling M (2013) ESMO guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). Ann Oncol 24(3):561–576. https://doi.org/10.1093/annonc/mds517

6. Salles G, Seymour JF, Offner F, Lopez-Guillermo A, Belada D, Xerri L, Feugier P, Bouabdallah R, Catalano JV, Brice P, Caballero D, Haioun C, Pedersen LM, Delmer A, Simpson D, Leppa S, Soubeyran P, Hagenbeek A, Casasnovas O, Intragumtornchai T, Ferme C, da Silva MG, Sebban C, Lister A, Estell JA, Milone G, Sonet A, Mendila M, Coiffier B, Tilly H (2011) 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 377(9759):42–51. https://doi.org/10.1016/S0140-6736(10)62175-7
7. (NCCN) NCCN (2018) NCCN clinical practice guidelines in oncology. B-Cell Lymphomas Version 2:2018
8. Dreyling M, Thieblemont C, Gallamini A, Arcaini L, Campo E, Hermine O, Kluin-Nelemans JC, Ladetto M, Le Gouill S, Iannitto E, Pileri S, Rodriguez J, Schmitz N, Wotherspoon A, Zinzani P, Zucca E (2013) ESMO consensus conferences: guidelines on malignant lymphoma. Part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. Ann Oncol 24(4):857–877. https://doi.org/10.1093/annonc/mds643
9. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catala-Lopez F, Gotzsche PC, Dickersin K, Boutron I, Altman DG, Moher D (2015) The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 162(11):777–784. https://doi.org/10.7326/m14-2385
10. Chihara D, Ito H, Matsuda T, Shibata A, Katsumi A, Nakamura S, Tomotaka S, Morton LM, Weisenburger DD, Matsuo K (2014) Differences in incidence and trends of haematological malignancies in Japan and the United States. Br J Haematol 164(4):536–545. https://doi.org/10.1111/bjh.12659
11. Chouhan J, Batra S, Gupta R, Guha S (2016) Gastrointestinal follicular lymphoma: using primary site as a predictor of survival. Cancer Medicine 5(10):2669–2677. https://doi.org/10.1002/cam4.763
12. Khalil MO, Morton LM, Devesa SS, Check DP, Curtis RE, Weisenburger DD, Dores GM (2014) Incidence of marginal zone lymphoma in the United States, 2001-2009 with a focus on primary anatomic site. Br J Haematol 165(1):67–77. https://doi.org/10.1111/bjh.12730
13. Kuper-Hommel MJJ, Van De Schans SAM, Vreugdenhil G, Van Krieken JHJM, Coebergh JWW (2013) Trends in incidence, therapy and outcome of localized nodal and extranodal marginal zone lymphomas: declining incidence and inferior outcome for gastrointestinal sites. Leuk Lymphoma 54(9):1891–1897. https://doi.org/10.3109/10428194.2013.764421
14. Le Guyader-Peyrou S, Belot A, Maynadie M, Binder-Foucard F, Remontet L, Troussard X, Bossard N, Monnereau A (2016) Cancer incidence in France over the 1980-2012 period: hematological malignancies. Revue d'Epidemiologie et de Sante Publique 64(2):103–112. https://doi.org/10.1016/j.respe.2015.12.017
15. Liu L, Wang H, Chen Y, Rustveld L, Liu G, Du XL (2013) Splenic marginal zone lymphoma: a population-based study on the 20012008 incidence and survival in the United States. Leuk Lymphoma 54(7):1380–1386. https://doi.org/10.3109/10428194.2012.743655
16. Luminari S, Cesaretti M, Marcheselli L, Rashid I, Madrigali S, Maiorana A, Federico M (2010) Decreasing incidence of gastric MALT lymphomas in the era of anti-helicobacter pylori interventions: results from a population-based study on extranodal marginal zone lymphomas. Ann Oncol 21(4):855–859. https://doi.org/10.1093/annonc/mdp402
17. Olszewski AJ, Castillo JJ (2013) Survival of patients with marginal zone lymphoma: analysis of the surveillance, epidemiology, and end results database. Cancer 119(3):629–638. https://doi.org/10.1002/cncr.27773
18. Smith A, Crouch S, Lax S, Li J, Painter D, Howell D, Patmore R, Jack A, Roman E (2015) Lymphoma incidence, survival and prevalence 2004-2014: sub-type analyses from the UK's Haematological Malignancy Research Network. Br J Cancer 112(9):1575–1584. https://doi.org/10.1038/bjc.2015.94
19. Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR (2016) 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin 66(6):443–459. https://doi.org/10.3322/caac.21357
20. Van Leeuwen MT, Turner JJ, Joske DJ, Falster MO, Srasuebkul P, Meagher NS, Grulich AE, Giles GG, Vajdic CM (2014) Lymphoid neoplasm incidence by WHO subtype in Australia 1982-2006. Int J Cancer 135(9):2146–2156. https://doi.org/10.1002/ijc.28849
21. Beveridge R, Satram-Hoang S, Sail K, Darragh J, Chen C, Forsyth M, Reyes C (2011) Economic impact of disease progression in follicular non-Hodgkin lymphoma. Leuk Lymphoma 52(11):2117–2123. https://doi.org/10.3109/10428194.2011.592623
22. Conconi A, Lobetti-Bodoni C, Montoto S, Lopez-Guillermo A, Coutinho R, Matthews J, Franceschetti S, Bertoni F, Moccia A, Rancoita PMV, Gribben J, Cavalli F, Gaidano G, Lister TA, Montserrat E, Ghielmini M, Zucca E (2015) Life expectancy of young adults with follicular lymphoma. Ann Oncol 26(11):2317–2322. https://doi.org/10.1093/annonc/mdv376
23. Gangatharan SA, Maganti M, Kuruvilla JG, Kukreti V, Tiedemann RE, Gospodarowicz MK, Hodgson DC, Sun A, Tsang RW, Pintilie M, Crump M (2015) Clinical characteristics and early treatment outcomes of follicular lymphoma in young adults. Br J Haematol 170(3):384–390. https://doi.org/10.1111/bjh.13451
24. Hirayama Y, Ishitani K, Ota S, Kurosawa M, Kondo T, Takimoto R, Mori A, Sakai H, Torimoto Y, Yamamoto S, Sato K, Iwasaki H, Kohda K, Ishida T, Kakinoki Y, Fukuhara T, Kato J (2014) Long-term survey of survival time, histological transformation, and secondary malignancies in Japanese patients with advanced-stage follicular lymphoma in the rituximab era: Hokkaido Hematology Study Group. Int J Hematol 100(3):281–289. https://doi.org/10.1007/s12185-014-1629-4
25. Nabhan C, Byrtek M, Rai A, Dawson K, Zhou X, Link BK, Friedberg JW, Zelenetz AD, Maurer MJ, Cerhan JR, Flowers CR (2015) Disease characteristics, treatment patterns, prognosis, outcomes and lymphoma-related mortality in elderly follicular lymphoma in the United States. Br J Haematol 170(1):85–95. https://doi.org/10.1111/bjh.13399
26. Prochazka V, Papajik T, Janikova A, Belada D, Kozak T, Salek D, Sykorova A, Mocikova H, Campr V, Dlouha J, Langova K, Furst T, Trneny M (2016) Frontline intensive chemotherapy improves outcome in young, high-risk patients with follicular lymphoma: pair-matched analysis from the Czech Lymphoma Study Group Database. Leukemia & Lymphoma 1–13. https://doi.org/10.1080/10428194.2016.1213834
27. Pulte D, Gondos A, Brenner H (2012) Expected long-term survival of older patients diagnosed with non-Hodgkin lymphoma in 2008-2012. Cancer Epidemiol 36(1):e19–e25. https://doi.org/10.1016/j.canep.2011.08.006
28. Lenglet J, Traulle C, Mounier N, Benet C, Munoz-Bongrand N, Amorin S, Noguera ME, Traverse-Glehen A, Ffrench M, Baseggio L, Felman P, Callet-Bauchu E, Brice P, Berger F, Salles G, Briere J, Coiffier B, Thieblemont C (2014) Long-term follow-up analysis of 100 patients with splenic marginal zone lymphoma treated with splenectomy as first-line treatment. Leuk Lymphoma 55(8):1854–1860. https://doi.org/10.3109/10428194.2013.861067
29. Danese MD, Reyes CM, Gleeson ML, Halperin M, Skettino SL, Mikhael J (2016) Estimating the population benefits and costs of

rituximab therapy in the United States from 1998 to 2013 using real-world data. Med Care 54(4):343–349. https://doi.org/10.1097/MLR.0000000000000486
30. Griffiths RI, Gleeson ML, Mikhael J, Danese MD (2015) Impact on medical cost, cumulative survival, and cost-effectiveness of adding rituximab to first-line chemotherapy for follicular lymphoma in elderly patients: an observational cohort study based on SEER-Medicare. Br J Haematol 170(3):384-390. https://doi.org/10.1111/bjh.13451
31. Horsboel TA, Nielsen CV, Nielsen B, Jensen C, Andersen NT, de Thurah A (2013) Type of hematological malignancy is crucial for the return to work prognosis: a register-based cohort study. J Cancer Surviv 7(4):614–623. https://doi.org/10.1007/s11764-013-0300-z
32. Maurer MJ, Bachy E, Ghesquieres H, Ansell SM, Nowakowski GS, Thompson CA, Inwards DJ, Allmer C, Chassagne-Clement C, Nicolas-Virelizier E, Sebban C, Lebras L, Sarkozy C, Macon WR, Feldman AL, Syrbu SI, Traverse-Glehan A, Coiffier B, Slager SL, Weiner GJ, Witzig TE, Habermann TM, Salles G, Cerhan JR, Link BK (2016) Early event status informs subsequent outcome in newly diagnosed follicular lymphoma. Am J Hematol 91(11):1096–1101. https://doi.org/10.1002/ajh.24492
33. Migdady Y, Salhab M, Dang NH, Markham MJ, Olszewski AJ (2016) Disparities in conditional net survival among non-Hodgkin lymphoma survivors: a population-based analysis. Leuk Lymphoma 57(3):676–684. https://doi.org/10.3109/10428194.2015.1102246
34. Monnereau A, Troussard X, Belot A, Guizard AV, Woronoff AS, Bara S, Lapotre-Ledoux B, Iwaz J, Tretarre B, Maynadie M (2012) Unbiased estimates of long-term net survival of hematological malignancy patients detailed by major subtypes in France. Int J Cancer 132(10):2378–2387. https://doi.org/10.1002/ijc.27889
35. Mounier M, Bossard N, Belot A, Remontet L, Iwaz J, Dandoit M, Girard-Boulanger S, Herry A, Woronoff AS, Casasnovas RO, Maynadie M, Giorgi R (2015) Trends in excess mortality in follicular lymphoma at a population level. Eur J Haematol 94(2):120–129. https://doi.org/10.1111/ejh.12403
36. Nabhan C, Zhou X, Day BM, Dawson K, Zelenetz AD, Friedberg JW, Cerhan JR, Link BK, Flowers CR (2016) Disease, treatment, and outcome differences between men and women with follicular lymphoma in the United States. Am J Hematol 91(8):770–775. https://doi.org/10.1002/ajh.24401
37. Nakamura S, Sugiyama T, Matsumoto T, Iijima K, Ono S, Tajika M, Tari A, Kitadai Y, Matsumoto H, Nagaya T, Kamoshida T, Watanabe N, Chiba T, Origasa H, Asaka M (2012) Long-term clinical outcome of gastric MALT lymphoma after eradication of Helicobacter pylori: a multicentre cohort follow-up study of 420 patients in Japan. Gut 61(4):507–513. https://doi.org/10.1136/gutjnl-2011-300495
38. Olszewski AJ, Castillo JJ (2013) Comparative outcomes of oncologic therapy in gastric extranodal marginal zone (MALT) lymphoma: analysis of the SEER-Medicare database. Ann Oncol 24(5):1352–1359. https://doi.org/10.1093/annonc/mds644
39. Olszewski AJ, Ali S (2014) Comparative outcomes of rituximab-based systemic therapy and splenectomy in splenic marginal zone lymphoma. Ann Hematol 93(3):449–458. https://doi.org/10.1007/s00277-013-1900-4
40. Servitje O, Muniesa C, Benavente Y, Monsalvez V, Garcia-Muret MP, Gallardo F, Domingo-Domenech E, Lucas A, Climent F, Rodriguez-Peralto JL, Ortiz-Romero PL, Sandoval J, Pujol RM, Estrach MT (2013) Primary cutaneous marginal zone B-cell lymphoma: response to treatment and disease-free survival in a series of 137 patients. J Am Acad Dermatol 69(3):357–365. https://doi.org/10.1016/j.jaad.2013.04.047
41. Stathis A, Chini C, Bertoni F, Proserpio I, Capella C, Mazzucchelli L, Pedrinis E, Cavalli F, Pinotti G, Zucca E (2009) Long-term outcome following Helicobacter pylori eradication in a retrospective study of 105 patients with localized gastric marginal zone B-cell lymphoma of MALT type. Ann Oncol 20(6):1086–1093. https://doi.org/10.1093/annonc/mdn760
42. van de Schans SAM, van Steenbergen LN, Coebergh JWW, Janssen-Heijnen MLG, van Spronsen DJ (2014) Actual prognosis during follow-up of survivors of B-cell non-Hodgkin lymphoma in the Netherlands. Haematologica 99(2):339–345. https://doi.org/10.3324/haematol.2012.081885
43. Pettengell R, Donatti C, Hoskin P, Poynton C, Kettle PJ, Hancock B, Johnson S, Dyer MJS, Rule S, Walker M, Wild D (2008) The impact of follicular lymphoma on health-related quality of life. Ann Oncol 19(3):570–576. https://doi.org/10.1093/annonc/mdm543
44. Carter G, Liepa A, Zimmermann A, Morschhauser F (2008) Validation of the functional assessment of cancer therapy–lymphoma (FACT-LYM) in patients with relapsed/refractory mantle cell lymphoma. Paper presented at the American Society of Hematology
45. Oerlemans S, Issa DE, van den Broek EC, Nijziel MR, Coebergh JWW, Mols F, van de Poll-Franse LV (2014) Impact of therapy and disease-related symptoms on health-related quality of life in patients with follicular lymphoma: results of the population-based PHAROS-registry. Eur J Haematol 93(3):229–238. https://doi.org/10.1111/ejh.12335
46. Tan D, Horning SJ, Hoppe RT, Levy R, Rosenberg SA, Sigal BM, Warnke RA, Natkunam Y, Han SS, Yuen A, Plevritis SK, Advani RH (2013) Improvements in observed and relative survival in follicular grade 1-2 lymphoma during 4 decades: the Stanford University experience. Blood 122(6):981–987. https://doi.org/10.1182/blood-2013-03-491514