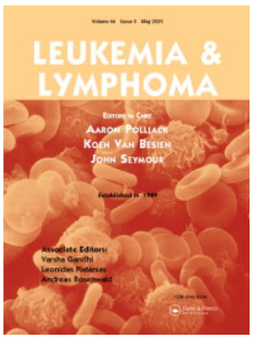

Leukemia & Lymphoma

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ilal20

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To cite this article: Pasquale L. Fedele & Stephen Opat (28 Jan 2025): Indolent lymphoma: addressing the needs of survivors, Leukemia & Lymphoma, DOI: 10.1080/10428194.2025.2456970

To link to this article: https://doi.org/10.1080/10428194.2025.2456970

Published online: 28 Jan 2025.

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2025.2456970

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Indolent lymphoma: addressing the needs of survivors

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ABSTRACT

Over the past two decades, there has been a continuous improvement in outcome for patients with indolent lymphoma (iNHL) resulting in a gradual accumulation of survivors. While life expectancy in the current era approaches that of the lymphoma-free population, patients continue to experience lifelong complications of the disease and its treatment affecting general health, emotional, psychological and social wellbeing, relationships, employment, finances, and fitness. Contemporary care models while suited to the management of lymphoma are often lacking when it comes to identification and management of these additional needs. Given improvements in physical survival achieved over the past decades, it is timely for us to focus on other issues affecting patient wellbeing including immunodeficiency and infection, second cancers, cardiovascular disease, bone health, psychological wellbeing, and sexual health. Many of these aspects are in the domain of the primary care physician; however, there is limited guidance on how these issues should be addressed. It is now time for us to engage our patients, their caregivers, and other healthcare providers in care aspects beyond the lymphoma diagnosis, so they can anticipate a rich and full life, free from both direct and indirect consequences of the lymphoma diagnosis.

ARTICLE HISTORY
Received 13 November 2024
Revised 1 January 2025
Accepted 17 January 2025

KEYWORDS
Indolent lymphoma; Chronic lymphocytic leukemia; CLL; follicular lymphoma; Marginal zone lymphoma; Waldenström's macroglobulinemia; Lymphoplasmacytic lymphoma; survivorship care

While the overall incidence of non-Hodgkin lymphoma (NHL) has plateaued, improvements in therapy have led to a gradual accumulation of survivors [1–4]. In the UK, 5-year relative survival for CLL has increased from 82.8% in 2005–2009 to 90.7% in 2018–2019, with similar improvements reported for marginal zone lymphoma (MZL), follicular lymphoma (FL), and mantle cell lymphoma (MCL), increasing from 75.8 to 86.0%, 82.5 to 86.9%, and 34.3 to 52.9%, respectively [5]. In Australia, the 5-year overall survival in FL increased from 73% to 86% [6]. Much of this improvement predates the introduction of novel agents and is likely attributable to rituximab [6,7].

While survival for chronic lymphocytic lymphoma (CLL)/small lymphocytic lymphoma (SLL) and other indolent lymphoma (iNHL) subtypes has improved, relative mortality increases rapidly after age 75 years, suggesting an increased sensitivity to disease and treatment in older individuals, emphasizing the need for survivorship care in older adults [1,8].

In FL, progression of lymphoma remains one of the most common causes of death accounting for 45% of identifiable mortality. Complications of therapy and second primary malignancies (SPMs) each account for roughly 10% of mortality in one series [9]. A French/US study of FL performed in the rituximab era also identified lymphoma as the most common cause of death, 55% occurring in those with histologic transformation. However, 48% of treatment related deaths were due to infection, 29% due to myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), and 14% due to cardiotoxicity [10].

A study of iNHL (excluding FL and SLL), identified lymphoma-related mortality of 8.0% versus 13.6% due to other causes. The lymphoma-related deaths varied by subtype, ranging from 3.7% in extranodal MZL compared to 19.3% in lymphoplasmacytic lymphoma (LPL)/Waldenström macroglobulinemia (WM) [11]. In MZL, approximately 40% of death events were related to lymphoma, with cardiovascular disease (CVD) accounting for 20%, other malignancies 14%, and lung pathology (5%) [12,13].

Similarly, most patients diagnosed with CLL in the current era will die from non-CLL-related causes, including second cancers, vascular disease, and infection. A study of 1274 patients from the Mayo Clinic identified the cause of death as CLL progression in 35%, infection in 6%, second malignancy in 16%, and

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other unrelated conditions, including CVD, stroke, dementia, lung disease, and renal disease in 21% [14].

Survivorship care in indolent lymphomas

Survivorship care aims to deliver a holistic approach to address the short- and long-term health effects of cancer and cancer-treatment. This includes both physical late effects, such as the risk of secondary malignancies, cardio-pulmonary, metabolic and immune/infective consequences, as well as psychosocial. A high priority is given to the promotion of a healthy lifestyle and preventative health and aims to assist patients returning to and maintaining a fulfilling life. Care coordination is a key tenet. Traditionally survivorship care has been limited to 'survivors' of curable malignancies who have completed treatment of finite duration. However, the importance of this holistic approach is now recognized in those with incurable malignancies [15], including CLL [16]. Patients with CLL or iNHLs suffer chronic multisystem physical and psychosocial effects, driven directly or indirectly by their disease, as well as therapy. These require specific attention by treating clinicians and broader planning for health service delivery.

Here, we define the specific key health domains and provide guidance for a survivorship and chronic disease model of care (Table 1).

Cardiovascular disease

For older patients with blood cancer, CVD is the leading cause of death after progression of their primary malignancy [27]. A large meta-analysis including 178,602 patients with hematological malignancy (HM) and 1,781,212 controls identified an increased risk of acute myocardial infarction (AMI), heart failure (HF), and stroke with standardized incidence ratios (SIRs) of 1.65 [1.29–2.09], 4.82 [3.72–6.25], and 1.60 [1.29–2.09], respectively. Similarly, a large New Zealand primary care study also identified an increased risk of CVD in NHL survivors with an SIR of 1.90 [1.42–2.54] [28].

In patients with CLL, a history of CVD has been reported in 32% at CLL diagnosis and 37% at the time of first therapy [29].

The etiology of the increased cardiovascular risk is complex, but anti-lymphoma therapy, particularly anthracyclines, kinase inhibitors such as Bruton tyrosine kinase inhibitor (BTKi), stem cell transplantation, and radiotherapy to the mediastinum and other vascular sites are likely causative [30]. The cardiovascular risks of BTKi including hypertension, HF, atrial and ventricular arrhythmia are well described with lower rates of arrhythmia observed with second generation BTKi's. Heart failure appears to be solely associated with use of ibrutinib [31].

Studies quantifying anthracycline-induced cardiomyopathy (AIC) risk by specific lymphoma subtype are sparse. A large contemporary study of 2625 patients treated with anthracyclines (28% NHL) with a median follow-up of 5.2 years identified incident cardiotoxicity (defined as LVEF decrease >10 absolute points, and <50%) in 6.2% of patients with NHL [32]. Pooled analyses of patients receiving CHOP/R-CHOP for various forms of lymphoma demonstrate that the elderly are more prone to develop high-grade cardiovascular adverse events, and risk increases according to the number of cycles of chemotherapy administered and the presence of preexisting cardiac disease [33,34]. These results are underpinned by the observation of a high prevalence of cardiovascular risk factors in lymphoma patients ≥65 years, where 73% of patients had hypertension, 54% hyperlipidemia, and 32% diabetes mellitus [33]. Importantly, with early diagnosis and intervention, AIC is potentially reversible [32].

Comprehensive cardiac assessment prior to commencement of BTKi and anthracyclines, as well as subsequent surveillance, is strongly recommended as is advice regarding optimization of cardiac risk factors and healthy lifestyle [18,31]. Given the high baseline prevalence of CVD in patients with CLL and iNHL, ongoing cardiological follow-up after the conclusion of therapy should be considered for all patients.

Infection

Patients with iNHL have increased risk of infections caused by both the disease and anticancer therapy. Patients have a complex immune dysfunction, both evident at early stage, and due to therapy [35]. It is characterized by an increase in regulatory T cells and inhibitory cytokines and decreased proliferative capacity of effector cells in comparison to memory cells [36]. There are also a higher proportion of activated T cells expressing markers associated with T cell exhaustion [37]. Hypogammaglobulinemia is a common finding both at presentation and due to therapy [38].

It is also now recognized that some patients have a preexisting immune deficiency resulting in cancer susceptibility. Several primary immune deficiencies including: (severe) combined immune deficiency, common variable immunodeficiency, activated PI3Kinase δ syndrome, and autoimmune lymphoproliferative syndrome have been associated with an increased risk of developing lymphoma. The diagnosis of lymphoma in a younger patient and presence of immunodeficiency or autoimmune disease may be a clue to the diagnosis [39].

Table 1. Key health domains and survivorship recommendations in CLL and indolent lymphomas.

Domain	Recommendations	Strength of recommendation[a]	Level of evidence[a]
Cardiovascular disease	Modifiable risk factors		
	Regular physical activity and advice regarding nutrition and diet as per international cardiovascular primary prevention guidelines [17].	2	C-LD
	Optimal control of modifiable cardiac risk factors such as hypertension, dyslipidemia and diabetes mellitus.	2	C-LD
	BTK inhibitors [18]		
	Cardiovascular assessment (including BP measurement and pulse-taking (or ECG rhythm strip) should be conducted at every visit.	2	C-LD
	Weekly home BP monitoring for three months, followed by monthly monitoring should be considered.	2	C-EO
	Transthoracic echocardiogram recommended in all high-risk patients at baseline and in all patients that develop AF.	2	C-EO
	Anthracycline induced cardiomyopathy	1	See reference
	We refer readers to the recently updated, comprehensive ESC guidelines on cardio-oncology [18]		
	Early referral to a cardiologist/cardio-oncology service.	2b	C-EO
Immunity and infections	Vaccinations as per consensus guidelines (e.g. [19,20]), preferably before treatment or during maintenance (although poor vaccine responses are well described in CLL and iNHL).		
	Annual inactivated influenza vaccine	1	B-NR
	Pneumococcal vaccine (pneumococcal conjugate vaccine, followed by pneumococcal polysaccharide 23-valent vaccine ≥2 months later).	1	B-NR
	COVID-19 vaccination as per local guidelines.	1	B-NR
	Recombinant varicella zoster virus vaccine [21]	1	B-NR
	Consider other inactive vaccines (including respiratory syncytial virus, hemophilus influenzae B, human papilloma virus, and hepatitis B vaccine) as per age, comorbidities and local recommendations, 3–6 months following treatment.	1	B-NR
	Avoidance of live vaccines.	1	C-LD
	Consideration of IVIg/SCIg in patients with hypogammaglobulinemia and severe/recurrent bacterial infection.	2	B-R
Secondary malignancy	Preventative measures:		
	Cessation of smoking [22], avoidance of excessive alcohol consumption, adherence to sun protection guidelines.	1	A
	Age based screening programs guided by personal and family history, radiation exposure and other risk factors		
	Skin cancer surveillance [23]	1	C-LD
	Fecal occult blood testing (colonoscopy in high risk).	1	A
	Breast cancer screening program (mammography).	1	A
	Cervical screening (Pap-smears).	1	A
	Prostate cancer screening (PSA) as per local guidelines (not universally recommended in asymptomatic men).	2	C-EO
Bone disease	Optimization of vitamin D and calcium status.	2	C-LD
	Weight bearing exercise.	2	C-LD
	Bone densitometry screening in patients with high corticosteroid exposure or other risk factors.	2	C-LD
	Early referral to metabolic bone clinic/commencement of antiresorptive therapy.	2	C-LD
Frailty	Treatment of underlying CLL/iNHL [24]	1	B-R
	A geriatric assessment (e.g. PGA) should be performed on all patients >65 yo and updated at key milestones [25].	1	B-R
	Motivate patients to maintain regular exercise, including aerobic exercise and resistance exercise for all major muscle groups.	2	C-LD
	Consider exercise physiology referral.	2	C-EO
	Occupational therapy and physiotherapy referral as required.	2	C-EO
Psychological and emotional	Screening (PGA, or other tools including HADS, PHQ-9, GAD-7, distress thermometer, and targeted history) at diagnosis and at regular intervals, particularly at times of change of disease status and management.	2	C-EO
	Early psychology referral (preferably with cancer/chronic disease expertise).	2	C-EO
	Involvement with patient's primary care physician.	2	C-EO
	Provide information on local disease peer support groups.	2	C-EO
	Carer support	2	C-EO
	Screen for impaired sexual health and impact on relationships.	2	C-EO
Social and financial	Early social work referral.	2	C-EO
Education and information	Provision of (linguistically appropriate) disease-specific patient information.	2	C-EO
	Care-coordination.	2	C-EO
	Involvement of family in consults (with patient consent), particularly when change of disease status or management plan.	2	C-EO
	Provide information on local cancer support services.	2	C-EO
Dentition	At least annual dental review.	2	C-EO
	Education regarding optimal dental hygiene.	2	C-EO

Adapted from Fedele and Opat [16].

Strength of recommendation. Class 1 (strong) – benefit ⋙ risk. Class 2a (moderate) – benefit ≫ risk. Class 2b (weak) – benefit > risk. Class 3: no benefit (moderate) – benefit = risk. Class 3: harm (strong) – risk > benefit.

Quality of evidence. Level A – (1) High-quality evidence from more than one RCT. (2) Meta-analyses of high-quality RCTS. (3) One of more RCTS corroborated by high-quality registry studies. Level B-R (randomized) – (1) moderate-quality evidence from one or more RCTS. (2) Meta-analyses of moderate-quality RCTs. Level B-NR (nonrandomized) – (1) moderate-quality evidence from one or more well-designed, well executed nonrandomized studies, observational studies, or registry studies. (2) Meta-analyses of such studies. Level C-LD (limited data) – (1) randomized or nonrandomized observational or registry studies with limitations of design or execution. (2) Meta-analyses of such studies. (3) Physiological or mechanistic studies in human subjects. Level C-EO (expert opinion) – (1) consensus of expert opinion based on clinical experience.

[a]Grading of strength of recommendations and level of evidence has been conducted as per Kleindorfer et al. [26].

BTK, Bruton's tyrosine kinase. BP, blood pressure. ECG, electrocardiogram. AF, atrial fibrillation. ESC, European Society of Cardiology. CLL, chronic lymphocytic leukemia. INHL, indolent non-Hodgkin's lymphoma. IVIg, intravenous immunoglobulin. SCIg, subcutaneous immunoglobulin. PGA, practical geriatric assessment. HADS, hospital anxiety and depression scale. PHQ-9, patient health questionaire-9. GAD-7, general anxiety disorder-7. RCT, randomized controlled trial.

Infection rates prior to treatment commencement have been reported to be increased above healthy controls (11.66 vs. 7.13 infections per 1000 days) including higher rates of hospitalization (5% vs. 2%), a marker of severe infection. Even those without hypogammaglobulinemia were at higher risk [40]. A Danish registry study including over 30,000 patients showed an increased rate of antibiotic prescribing up to 15 years prior to diagnosis in patients with CLL, MZL, and LPL (but not FL). Prescription of two or more antimicrobials in the year prior to diagnosis was associated with shorter survival [41].

While control of iNHL can improve immune function, continuously administered therapy can restrict immune responses in an ongoing manner. Anti-CD20 antibodies are well understood to decreased antibody production. In FL, the use of CD20 antibodies was associated with a 45% risk of hypogammaglobulinemia with 10% becoming symptomatic [42]. Use of CD20 antibodies has been associated with poor vaccine responses, reactivation of hepatitis B and cytomegalovirus (in combination with bendamustine) and rarely, progressive multifocal leucoencephalopathy due to John Cunningham (JC) virus reactivation [43–45].

There are few studies on the dynamics of immune recovery after chemoimmunotherapy, but restoration of immunoglobulin and T cells after CD20 antibody containing regimens has been shown to take 2 years or more [36].

A post hoc analysis of the GALLIUM study comparing frontline chemotherapy with either obinutuzumab or rituximab in patients with FNHL showed higher rates of grade 3–5 infections occurring during the maintenance (14.7% vs. 5.2%) and follow-up (5.8% vs. 1.9%) phases in those who received bendamustine rather than CHOP or CVP-based therapy [46]. Furthermore, an Australian study, examining bendamustine in patients with iNHL identified near universal lymphopenia, with 44% infection (50% bacterial) resulting in 27% hospitalization. Nearly, one-third of infections occurred more than 3 months after completion of bendamustine. Use of *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis, mainly trimethoprim/sulfamethoxazole halved the rate of bacterial infection and use of antiviral prophylaxis, mainly valaciclovir was associated with fewer varicella zoster virus (VZV) and herpes simplex virus (HSV) infections [47].

Bispecific antibodies (BSAbs), which form an immune synapse between effector T cells and CD19 or CD20 on tumor cells, are an emerging class of anti-lymphoma agents, with approval in several jurisdictions. A recent meta-analysis identified infections of any grade occurring in 44% of patients, of which 3% was fatal. COVID19 was the most common fatal infection with a few deaths attributable to either PJP or bacterial infection. Risk of infection in patients with iNHL was higher in patients with relapsed or refractory disease than in the frontline [48]. Treatment emergent hypogammaglobulinemia is infrequently reported in BSAb studies, but is likely to be high, with the kinetics of B cell/antibody recovery poorly described [48].

While patients with CLL and iNHL may display diminished vaccine responses to influenza, *Streptococcus pneumoniae*, varicella zoster, and SARS-CoV-2, compared to healthy individuals, protective humoral responses are often observed. Therapy with B cell targeting agents is strongly associated with impaired responses, but these negative effects diminish over time, although vaccine non-responsiveness has been reported for up to 2 years following CAR T therapy [49]. The loss of follicular T-helper cells (Tfh) in blood has also associated with nonresponse. The contribution of T cell immunity to vaccine responses is poorly characterized but likely also to provide a degree of protection against pathogens [49].

Untreated patients may benefit from vaccination either at diagnosis or far in advance of treatment with the time required to initiate a humoral response before initiation of B-cell-targeting therapies being defined but likely several weeks [49].

A study of patient's concerns conducted during the coronavirus disease (COVID-19) pandemic identified increased apprehension in 75% with specific concerns about getting infected while in hospital (32%), delays in treatment (21%), risk of infection from family members (18%), and the need for social distancing (13%) [50].

Hypogammaglobulinemia has been reported in 12.5–18.8% of patients with CLL and iNHL at baseline with an additional 38.9% developing hypogammaglobulinemia after rituximab exposure [51]. There is a paucity of prospective clinical trials providing evidence for immunoglobulin replacement in CLL and iNHL. However, a large retrospective study involving 3960 patients diagnosed with CLL and 13,232 patients with NHL showed rates of severe infection and antimicrobial use were reduced after immunoglobulin replacement [52]. While immunoglobulin replacement may reduce infection risk there is little evidence that it impacts survival [53].

Vaccination as per local guidelines is strongly recommended (Table 1), as is evidence-based use of anti-microbial prophylaxis dictated by specific treatment. Intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg) replacement should be considered in patients with hypogammaglobulinemia

and recurrent/severe bacterial infections. However, the burden of hospital visits for IVIg and training for self-administration of subcutaneous immunoglobulin should also be considered.

Autoimmunity

Autoimmunity is a recognized association with the development of lymphoma, possibly due to chronic immune activation, genetic susceptibilities common to both conditions, and therapy. The association between reports of lymphoma and class of immunosuppressive agent has been examined FDA Adverse Event Reporting System. Drugs with the highest reporting odds ratio (ROR) for NHL included azathioprine (2.09, 95% CI 1.94–2.24) followed by methotrexate (1.90, 95% CI 1.82–1.98). Drugs with lowest ROR for NHL included adalimumab (0.62, 95% CI 0.59–0.65) followed by sirolimus (0.66, 95% CI 0.54–0.80), tacrolimus (0.78, 95% CI 0.73–0.84), and etanercept 0.8 (0.76–0.84) [54]. In contrast, a French registry study comparing anti-TNF agents showed higher rates of lymphoma in patients receiving adalimumab or infliximab than those treated with etanercept suggesting higher rates of lymphoma with monoclonal-antibody therapy than with soluble-receptor therapy [55].

Lymphomas of all types are known to be associated with autoimmune manifestations with abnormal antibody production including anti-erythrocyte, antiplatelet, anti-nuclear, anti-native DNA, antiphospholipid antibodies, and lupus anticoagulant [56]. In a study of 2503 patients with NHL, 108 (4.3%) had a recognized autoimmune disease, mostly commonly autoimmune cytopenia (71.3%), neurological disease (10.2%), kidney disease (6.5%), and systemic vasculitis (5.6%) [57]. Survival outcomes were significantly worse for patients with autoimmune disease even after matching by age, sex, and lymphoma subtype. Further work is needed to understand the additional impact of this complication [57].

Secondary malignancies

Patients with CLL and iNHL have significantly increased risk of SPMs, likely due to the underlying disease, therapy-related immune dysfunction, and exposure to DNA-damaging agents [58].

A Swedish population-based study of over 50,000 patients with NHL and 260,000 age- and sex-matched controls identified a 40% higher rate of solid-malignancies and fivefold increased rate of MDS/AML [59]. Similar numbers of high and low-grade NHL were included, with no observed difference in rates of SPM. In patients with FL, the risk of MDS/AML has been falling since 2009, associated with the introduction of biological agents such as rituximab and a change in therapeutic strategy. Conversely, a Dutch study of 13,652 patients with FL identified a 42% increased risk of SPM compared with the general population, with no difference seen in the pre- vs. post-rituximab era [58]. An SIR of 3.45 (95% CI 2.34–4.9) for MDS and 7.78 (95% CI 6.01–9.92) for AML were reported. Similar findings have also been reported in other contemporaneous studies [60,61].

Registry studies have also demonstrated that patients with CLL have increased risk of solid organ malignancies and MDS/AML [62–65]. Exposure to DNA-damaging agents is an important risk factor, with incidence of secondary malignancy of 32% including MDS/AML in 6.3%, in long-term follow-up of patients following fludarabine, cyclophosphamide, and rituximab [66].

Similarly, patients with WM have been found to have approximately a 50% increased risk of secondary malignancy compared to the general population [67,68], with a median time to SPM of 3.7 years and cumulative incidence of SPM of 10% at 5 years and 16% at 10 years in one study [67].

Despite the indolent nature of mucosa-associated lymphoid tissue (MALT) lymphomas, risk of SPMs is increased, with a US SEER database study of 12,500 patients identifying occurrence of SPM in 11.7% of patients, 55% occurring within 5 years of diagnosis [69]. Risk of SPM is increased in patients with gastric MALT lymphomas, particularly following chemotherapy [70].

In addition to follow up for progression (and transformation) of their primary lymphoproliferative disease, clinicians should be mindful of the risk of SPMs. Patients should be counseled on preventative measures, such as smoking cessation, sun-protection, minimization of alcohol, and the importance of healthy diet and physical activity. Early detection and intervention are key, and patients should undergo regular age- and risk-factor guided cancer surveillance. Importantly, many national screening programs (such as breast, bowel, and cervical cancer screening) close at age 70–75. Given the older median age of diagnosis (FL 60-65, CLL 70.9, MZL 60, and WM 67) and improving survival, testing will need to be arranged outside of these programs for many patients. Patients with iNHL and CLL have been demonstrated to have significantly increased rates of skin cancers [58,71–73], particularly squamous cell carcinoma and melanoma. Patient

education and annual skin surveillance is therefore advised for all patients [74].

Osteoporosis and fracture risk

Patients with CLL and iNHL are at an increased risk of osteoporosis and fragility fractures. Etiological factors include advanced patient age at diagnosis; the direct impact of their disease on bone homeostasis, indirect impact through increased frailty, inactivity, and vitamin D deficiency; and importantly the effects of lymphoma therapy on bone homeostasis [75–78].

Several studies have demonstrated a reduction in bone mineral density (BMD) and increased fracture risk associated with chemotherapy and particularly corticosteroids [76,79,80]. In patients with FL, two recent studies have found a marked reduction in BMD from baseline and increase fracture risk in patients treated with R-CHOP, compared to patients who received bendamustine–rituximab, likely due to corticosteroid exposure [81,82].

While the impact of CLL/iNHL on bone homeostasis remains poorly understood, CLL cells have been shown to promote osteoclast differentiation and activation, through RANK ligand expression and secretion of bone remodeling cytokines including TNF, IL-6, and IL-11 [83–85]. In murine studies, introduction of CLL cells resulted in bone erosion that was prevented by denosumab (a RANKL inhibitor) [85]. Similarly, RANK ligand and vascular endothelial growth factor expression have been reported in iNHL complicated by destructive bone lesions [86]. Advanced disease has also been identified as a risk factor for loss of BMD and fractures [81].

A randomized phase III trial of bisphosphonate prophylaxis in patients with lymphomas (52% iNHL) during primary chemoimmunotherapy showed preservation of BMD in patients receiving zoledronic acid with studies of pamidronate and alendronate showing similar results [76,87,88]. Calcium and vitamin D supplementation should be considered for all patients, particularly pre-chemotherapy. Consideration should also be given to the use of bisphosphonates. Regular exercise should be encouraged to promote bone density, muscular strength and improved balance. Early identification and management of established osteoporosis is essential.

Frailty/QOL

With the median age of diagnosis being between 60 and 70 years, patients with iNHL and CLL have an increased risk of frailty due to physiological changes, medical comorbidities, and polypharmacy [89]. This is compounded by direct inflammatory and metabolic impact of their lymphoproliferative disease, reduction in physical activity and the adverse effects of therapy, particularly chemotherapy and corticosteroids. Consequently, CLL and iNHL are associated with a reduction in physical and psychological/social QOL, most pronounced in patients with advanced stage disease and at later lines of therapy [90–92].

Targeted therapies, with improved toxicity profile, may reduce the risk of frailty, as demonstrated in the frontline CLL HOVON139/GiVe trial which showed an objective improvement in frailty and QOL following venetoclax and obinutuzumab therapy [24].

Frailty is an independent risk factor for survival and impacts fitness for treatment and clinical trial eligibility. Importantly however, neither age or performance status (e.g. Eastern Cooperative Oncology Group Performance Status Scale (ECOG) or Karnofsky score) are adequate measures of frailty and specific frailty/geriatric assessments are required [89]. Recently updated American Society of Clinical Oncology (ASCO) guidelines recommend a geriatric assessment, such as the Practical Geriatric Assessment (PGA) be conducted on all patients older than 65 years (and targeted younger patients) receiving systemic cancer therapy [25].

An understanding of the individual's drivers of frailty and involvement of a multidisciplinary team composed of physiotherapists, exercise physiologists, occupational therapists, and nutritionists/dietitians is essential. There is increasing evidence supporting the benefit of exercise in cancer care, including survivorship [93,94]. Increased physical activity has been associated with improved overall and lymphoma-specific survival [95]; however, interventional studies are sparse.

Psychological/emotional impact

A diagnosis of an iNHL has both significant short- and long-term psychological impacts. In one study of newly diagnosed iNHL patients, 27.1% reported clinically significant anxiety and 14.6% post-traumatic stress disorder (PTSD) symptoms in the three months following diagnosis [96]. Major contributing factors include the incurable nature of their malignancy, indefinite time course, prognostic uncertainty, and lack of personal control of their illness [96]. Patients can experience both a loss of independence and increased isolation. Importantly, trauma symptoms are present in many patients in the absence of physical symptoms or active therapy and therefore screening and support for psychological distress, as well as helping develop

coping strategies and resilience are of high priority immediately from diagnosis. Improved emotional coping with prognosis has been associated with reduced incidence of anxiety, depression, and PTSD symptoms [96]. A 'watchful-waiting'/active surveillance initial treatment approach, commonly employed in newly diagnosed CLL and iNHL, is often discordant with patients' understanding and expectations around therapy, which potentially can also contribute to distress [97,98].

A retrospective review of a large US claims database of 36,054 patients with new diagnosis of iNHL (CLL/SLL = 19,891; FL = 9715; MCL = 1728; WM = 1738; MZL = 2982) identified a high rate of incident (19.4–25.7%) or prevalent (28.6–32.1%) mental health diagnosis in the 12 months following diagnosis [99]. This was predominantly anxiety (incidence 13.9–20.1%, total 30.9–38.2%), or depression (incidence 12.0–16.2%, total 27.5–31.9%). A mental health diagnosis was associated with higher healthcare resource utilization and costs.

A recent Danish registry study compared the use of psychotropic drugs (PDs) including antidepressants, anxiolytics, and antipsychotics, in 8750 patients with NHL and 43,750 age- and sex-match comparators [100]. NHL patients were found to have a higher two-year cumulative risk of PD use than comparators (16.4% vs. 5.1%, $p < .01$). PD use was initially higher for patients with aggressive NHL such as DLBCL (19.7%) compared with iNHL (13.1%), however at 5 years post diagnosis rates in of PD use in aggressive NHL approached that of the normal population, whereas patients with iNHL continued to be increased.

Treating physicians/teams should be mindful of the significant psychological impact of a CLL/iNHL diagnosis, from the time of diagnosis and irrespective of active treatment. Screening should be conducted at diagnosis and repeated at regular intervals, particularly at times of change of disease status and treatment. In addition to targeted history, we have previously suggested the use of validated screening tools such as the PGA [25], Hospital Anxiety and Depression Scale (HADS), Patient Health Questionaire-9 (PHQ-9), General Anxiety Disorder-7 (GAD-7), and the distress thermometer.

The important role played, burden placed, and psychological impact on spouses/partners and families, particularly those acting as carers, also needs consideration [101]. Clear and frequent communication with patients and their families is essential as well as providing information on relevant local cancer/lymphoma support services and peer support groups. Carers should be encouraged to look after their own physical and mental health and have regular contact with their general practitioner.

Sexual health

Given the older median age, impact on sexual health is often overlooked in patients with CLL and iNHL. While few studies have been conducted specifically in indolent disease, lymphoma patients treated with chemotherapy have been reported to have significantly impaired sexual health. Erectile dysfunction has been reported in 55% of male lymphoma survivors (severe in 14%) [102]. Greater risk of sexual dysfunction is seen with older age, greater number of comorbidities, worsened emotional distress, and presence of hypogonadism (lower testosterone/increased luteinizing hormone) [102,103]. Research in female patients is severely lacking. In one small study, sexual dysfunction attributed to lymphoma/therapy was reported in 50% of women (both pre- and post-menopause) [104], with specific domains including desire, lubrication, arousal, orgasm, and pain. Importantly, sexual dysfunction is associated with impaired QOL in both male and female patients [102,104]. Clearly greater research into this area, particularly in the era of novel therapies is needed. Screening for sexual dysfunction should be routine. A multidisciplinary approach is required, given the often complex etiology [105], which can include endocrine, neurological, and psychological factors, as well as general frailty. A discussion on fertility is not included, however in younger patients this of paramount importance.

Financial toxicity

Financial toxicity has been poorly studied in HM, particularly iNHLs. A recent systematic review including 55 studies using disparate and often non-standardized methods, identified between 20 and 50% of patients with HM reported some form of financial toxicity [106]. In contrast to 'survivors' of many other malignancies who have completed treatment of finite duration, patients with iNHLs have a chronic (lifelong), insidious, and often relapsing-remitting disease and treatment course and impact on lifestyle, occupation, and financial stability.

Given the median age of diagnosis, many patients are diagnosed around the time of retirement. Anecdotally, diagnosis of lymphoma and particularly commencement of treatment can be a trigger/driver of retirement. For younger patients, their disease, appointments, treatment, and episodes of illness, can impact their ability to consistently participate in the workforce and threaten their livelihood and financial trajectory.

While the introduction of oral targeted therapies has resulted in significant improvements in outcomes for patients with CLL and iNHL, they are associated with significantly higher out of pocket patient costs and overall per-patient lifetime treatment costs [107].

Changing therapeutic landscape of indolent lymphoma

While chemoimmunotherapy has been the prevailing treatment for iNHL, the therapeutic landscape is constantly changing. The long-term harmful effects of newer targeted therapies are anticipated to be less than chemoimmunotherapy; however, the risk of immunodeficiency is likely to be ever-present in chronically administered therapies and long-term risk of secondary cancer and CVD are unknown.

Since the introduction of rituximab, there has been a continuous change in therapeutic strategy in iNHL. Use of maintenance rituximab in FL was associated with prolongation of PFS however at a cost of increased infections [108], and chemoimmunotherapy with obinutuzumab was associated with an improvement in PFS in FL (but not MZL) at a cost of increased grade 3–5 adverse events (74.6% vs. 67.8%) and infections during maintenance (64.4 vs. 54.2%) [46].

Lenalidomide, an immunomodulatory agent with broad actions has been used for treatment of FL, MZL, and MCL [109,110]. While associated with an increase in SPMs in patients with myeloma, several trials in other indications (e.g. FL) did not report an increase [111]. Other side-effects can impact a patient's quality of life including fatigue, rash, diarrhea, and deep vein thrombosis [112].

EZH2 is an epigenetic regulator that induces transcriptional repression of target genes through methylation of histone H3. Tazemetostat, a drug targeting EZH2 has activity in both EZH2 wild type and mutated type FL leading to its approval for treatment in the third line or subsequently [113]. It is well tolerated with low rates of TEAE; however, myelodysplasia or acute myeloid leukemia has been reported in 0.7% of patients, with 2% stopping therapy due to SPMs. Consequently, the drug label contains an SPM warning [114].

BTK inhibitors have been examined in various iNHLs, including CLL/SLL, FL, MZL, and WM both as monotherapy and in combination with other agents [115–125]. Several studies show an association between BTKi use and upper respiratory tract infection and pneumonia. While uncommon, an increased risk of invasive fungal infections including *Cryptococcus* and *Aspergillus* species have been reported with more than half being fatal. There appears to be a similar risk across 1st and 2nd generation BTKi, all causing B-cell dysfunction along with off-target functional impairment of neutrophils and macrophages [126].

BTK inhibitors are also associated with hypertension and atrial arrhythmia. Randomized studies show a lower incidence of atrial arrhythmia with second-generation BTKis, zanubrutinib (5.2%), and acalabrutinib (9%) than with ibrutinib (13.3% and 16%, respectively). New-onset hypertension has been reported in up to 20% of patients with ibrutinib, which appears to be lower with acalabrutinib (9%) but not zanubrutinib (12–22%). New or worsened hypertension in patients receiving ibrutinib has been associated with increased risk of major cardiovascular events including myocardial infarction, stroke, HF, and cardiovascular death (HR, 2.17 [95% CI, 1.08–4.38]). Furthermore, patients with preexisting CVD have a nearly threefold higher rate of atrial arrhythmia (17% v 7%) and mortality (odds ratio [OR], 1.9 [95% CI, 1.06–3.41]) with ibrutinib and similarly second-generation BTKi. Initiation of antihypertensives was associated with a reduction in major adverse cardiovascular events [124,127–132].

The PI3Kinase delta inhibitors (idelalisib, copanlisib, duvelisib, and umbralisib) are highly active in several indolent histologies including CLL/SLL [133], MZL, and FL [134–137]. However, RCT have revealed high rates of severe adverse effects (infections, autoimmune hepatitis, and colitis) with concerning trends in reduced overall survival that has halted their clinical development in HM.

Several newer therapies have recently been approved in some jurisdictions or are in clinical development in low grade lymphoma including tafasitamab [138] (a monoclonal antibody directed against CD19), polatuzumab [139] (CD79b-directed antibody–drug conjugate), and loncastuximab tesirine [140] (CD19-directed antibody–drug conjugate). Magrolimab [141] (macrophage immune checkpoint inhibitor blocking CD47) (see Table 2). Reported toxicities (infusion reactions, cytopenia) are similar to other approved agents. Bispecific antibodies, such as mosunetuzumab [142], odronextamab [143], and epcoritamab [144] are also under investigation in relapsed indolent with toxicities including cytokine release syndrome (CRS) (an acute systemic inflammatory response), and immune effector cell-associated neurotoxicity syndrome (a potentially life-threatening neurotoxicity) in addition to cytopenia and infectious risk.

CAR-T cells (chimeric antigen receptor T cells) directed against CD19 or CD20 have an emerging role in low grade lymphoma, with recent FDA approval of axicabtagene ciloleucel [145], tisagenlecleucel [146], and lisocabtagene maraleucel [147] in relapsed/refractory FL (as well as RR CLL/SLL for lisocabtagene maraleucel, Table 2). While these agents are generally highly

Table 2. Recently approved immunotherapies in CLL/iNHL.

Agent	Trial	Year approved (FDA)	Indication
Mosunetuzumab	GO29781	2022	RRFL who have received two or more prior lines of systemic therapy
Epcoritamab	EPCORE NHL-1	2024	RR FL who have received two or more prior lines of systemic therapy
Odronextamab	ELM-2	2024	RR FL who have received two or more prior lines of systemic therapy
Axicabtagene ciloleucel	ZUMA-5	2021	RR FL who have received two or more prior lines of systemic therapy
Tisagenlecleucel	ELARA	2022	RR FL who have received two or more prior lines of systemic therapy
Lisocabtagene maraleucel	TRANSCEND	2024	RR FL who have received two or more prior lines of systemic therapy
Lisocabtagene maraleucel	TRANSCEND CLL 004	2024	CLL or SLL refractory to a BTK inhibitor and pretreated with a BCL-2 inhibitor

RR FL (please change the first RRFL to RR FL like the others), relapsed or refractory follicular lymphoma. CLL, chronic lymphocytic leukemia. SLL, small lymphocytic lymphoma. BTK, Bruton's tyrosine kinase.

of

efficacious, their cost and toxicity including CRS and immune effector cell associated-neurotoxicity syndrome (ICANS) may diminish their widespread application. Particularly as the long-term neurological consequences of severe ICANS and the sustained effects of CAR T cells on normal immune function remains to be determined. A recent review of non-relapse mortality (574 of 7604 cases) after CAR T therapy identified infection as the cause of death in over half (50.9%), followed by other malignancies (7.8%) and cardiovascular/respiratory events (7.3%) [148].

Given the life expectancy for most patients with iNHL is approaching normal, it is important that these newer agents' safety profile is similar or better than established therapies.

Sustainable models of survivorship care

While a cause for celebration, the increasing number of iNHL 'survivors' represents a significant healthcare burden. Over-stretched cancer physicians are ill-equipped to provide these aspects of care and multidisciplinary specialist-led survivorship clinics have capacity for only a limited number of high-risk patients. Sustainable strategies are required, which will need to be tailored to local health systems and individual patient needs.

Alternative models of survivorship care include: shared care – a collaborative approach involving both hospital specialist survivorship clinicians and the primary care physician; primary care provider-led care – survivorship care predominantly conducted in the primary care setting; nurse-led care – survivorship care directed by specialist nurses [149]. Importantly, multiple randomized trials/systematic reviews have found these models to be as effective as more resource intensive specialist-led survivorship services [150]. Irrespective of the model, effective integration of patients' primary care providers is essential. It is likely the optimal approach will include the empowerment individuals to take ownership of their survivorship care and long-term health and wellbeing [151].

Conclusions

There have been significant advances in the treatment of patients with CLL and iNHL over the last two decades, first with the introduction of immunotherapeutics such as rituximab and more recently with the development of novel agents targeting various molecular dependencies. While the number of lymphoma survivors continues to increase, very little attention has been given to their competing causes of mortality as well as physical and psychosocial morbidity, which remains increased compared with the general population and are often directly or indirectly driven by their disease and treatment. For many patients, a diagnosis will manifest as a lifelong multisystem relapsing-remitting chronic inflammatory condition and an appreciation of this, as well as the subsequent psychological and social impact on patients and their families is important. A holistic approach which empowers patients to be active participants in their survivorship care is paramount.

Acknowledgements

We are indebted to our survivors, Janne Williams and John Rogers for their critical review of the draft and whose lived experience assisted us in authoring this manuscript.

Author contributions

Manuscript writing: both authors. Final approval of manuscript: both authors.

Disclosure statement

Pasquale L. Fedele. Consulting or advisory role: Amgen, Pfizer, and Adaptive Biotechnologies. Research funding: Bristol Myers Squibb/Celgene (Inst). *Stephen Opat*. Honoraria: AbbVie,

AstraZeneca, Janssen, Roche, Gilead Sciences, Takeda, Merck, BeiGene, Ipsen, and Sanofi. Consulting or advisory role: AbbVie, AstraZeneca, Janssen, Novartis, Gilead Sciences, Takeda, Merck, BeiGene, and Ipsen. Research funding: AstraZeneca (Inst), BeiGene (Inst), Roche (Inst), AbbVie (Inst), Gilead Sciences (Inst), Takeda (Inst), Pharmacyclics (Inst), Janssen (Inst), Merck (Inst), Ipsen (Inst), and Novartis (Inst). Expert testimony: Antengene. Travel, accommodations, and expenses: EUSA Pharma.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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