REVIEW ARTICLE

Nodular lymphocyte-predominant Hodgkin lymphoma: advances in disease biology, risk stratification, and treatment

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Abstract

Recent updates have detailed how patients with nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) may be better risk stratified using prognostic scoring systems. Most patients with NLPHL present with early-stage disease and have an indolent disease course. To reflect these differences from classic Hodgkin lymphoma, nomenclature has been updated to recognize nodular lymphocyte-predominant B-cell lymphoma as an alternative to NLPHL. The Global NLPHL One Working Group have published their pivotal dataset in 2024 which challenges the prognostic significance of variant immunoarchitectural (IAP) patterns and proposes a new prognostic scoring system. Key identified prognostic factors include age >45 years, stage III-IV disease, hemoglobin <10.5 g/dL and splenic involvement. After multivariate analysis, variant IAP was not shown to be associated with inferior outcome. As most patients with NLPHL have excellent long-term survival, identifying patients where treatment de-escalation is appropriate will help to minimize toxicity. De-escalation strategies include observation after fully resected stage I disease, active surveillance, anti-CD20 antibody monotherapy, radiotherapy in early-stage disease, and avoiding anthracycline- or bleomycin-containing chemotherapy regimens. Evidence supporting the use of novel therapies remains limited with disappointing results from a recently published study of ibrutinib in patients with relapsed NLPHL. Hopefully, future trials will investigate novel agents such as checkpoint inhibitors, T-cell engaging antibodies and chimeric antigen receptor T-cell therapy.

Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare, indolent lymphoma traditionally considered a subtype of Hodgkin lymphoma. But it differs from classic Hodgkin lymphoma (cHL) with the malignant cells of NLPHL expressing B-cell antigens and most patients presenting with early-stage disease. Most patients experience excellent long-term survival despite the ongoing possibility of relapse.[1,2] To reflect these differences, the International Consensus Classification (ICC) of Mature Lymphoid Neoplasms has adopted the term nodular lymphocyte-predominant B-cell lymphoma (NLPBL). The 5th edition of the World Health Organization classification of hematolymphoid neoplasms continues to use the term NLPHL to align with ongoing trials and research whilst recognizing NLPBL as an acceptable alternative.[1,3]

This review aims to integrate advances in our understanding of molecular and genetic changes seen in NLPHL, prognostication with a summary of the recently proposed LP International Prognostic Score (LP-IPS), as well as an updated review of the evidence supporting various treatment regimens depending on stage, disease bulk, and risk factors present.

Epidemiology

Nodular lymphocyte-predominant Hodgkin lymphoma comprises only 5-13% of cases of HL.[4,5] There is a significant male predominance in Caucasians with 75% of patients being male, whilst this is less pronounced amongst other racial groups such as Black Americans where the male to

female ratio is 1.2:1.[6-8] NLPHL may occur at any age whilst in adults the median age of patients is between 35 to 40 years.[8,9] There is an increased risk of NLPHL in relatives of patients with NLPHL where germline alterations, such as deletion of the *NPAT* gene, may contribute.[10,11] Immune dysregulation might be important as associations with autoimmune lymphoproliferative syndrome and Hermansky-Pudlak type 2 syndrome have been described.[12,13] Certain human leukocyte antigen (HLA) subtypes may predispose patients to antigenic stimulation and lymphomagenesis as shown in an association between *Moraxella catarrhalis* infection and HLA-DRB1*04/07.[14]

Clinical presentation

Most patients with NLPHL have limited-stage disease. Stage I or II disease is seen in approximately 75% of patients.[2] Bulky disease of ≥10 cm is uncommon, present in only 1-2% of cases, whilst bulky disease ≥5 cm, which remains an adverse prognostic marker, is seen in up to 40%.[15,16] Typically, patients present with painless lymphadenopathy more commonly affecting peripheral lymph nodes, such as cervical or inguinal lymph nodes. A mediastinal mass is found in only 2-7% of patients compared to 60% of patients with cHL.[15-17] Constitutional symptoms are present in 15-20% of patients.[1] Extranodal involvement is uncommon with splenic involvement in 5%, hepatic involvement in 2-3%, and bone marrow involvement in 1-2% of patients[15]

Diagnosis

Morphology and immunophenotype

The morphology and immunophenotype of NLPHL are summarized in Table 1. The immunophenotype of LP cells helps to differentiate NLPHL from other disorders such as cHL. It is important to correlate the histologic findings with the clinical presentation as the presence of particular variant immunoarchitectural patterns (IAP) or possible disease transformation may influence treatment decisions, especially in the setting of aggressive clinical features. Figure 1 demonstrates typical histologic findings of a lymph node affected by NLPHL.

Variant immunoarchitectural patterns

The microscopic appearance of lymph node specimens can vary significantly between cases of NLPHL with differences in the degree of nodularity, distribution of LP cells, and background cell infiltrate. Fan *et al.* described six IAP (patterns A to F) to capture this, establishing typical (A and B) and variant (C to F) growth patterns.[18] In 75% of patients, a typical IAP is found where LP cells are predominantly found within B-cell rich nodules either in a "classic" nodular pattern (pattern A) or a serpiginous / interconnected nodular pattern (pattern B).

Variant IAP include cases where a variant growth pattern (patterns C-F) is present either as a major (>50% of lymphoma area) or minor (<50% of lymphoma area) component.[19] These IAP variants differ due to: prominent extranodular LP cells (pattern C); a predominant background of reactive T cells, either in nodules (pattern D) or diffusely (pattern E); or a B-cell-rich background but lacking the classic nodular pattern (pattern F). For a more detailed summary of the characteristics of each IAP, refer to *Online Supplementary Table S1*.

Recently, the Global NLPHL One Working (GLOW) Group published a large international retrospective study where 916 patients had available pathology to assess IAP.[2] A higher proportion of stage III or IV disease was noted in patients with IAP D and E whilst those with IAP F predominantly had early-stage disease and have a good prognosis.[2] More

Table 1. Summary of morphological and immunophenotypic features of nodular lymphocyte-predominant Hodgkin lymphoma.

Morphology
Effacement of normal lymph node architecture with a nodular infiltrate.
Infiltrate with small B lymphocytes, histiocytes, macrophages with scattered large LP cells.
Background lacks eosinophils, T cells or plasma cells typical of cHL.
LP cells, large malignant cells of NLPHL, have a single multilobulated nucleus.
PD1+ T cells commonly form a rosette around LP cells.
Immunohistochemistry
Nodular pattern highlighted by stains for FDC, i.e., CD21, CD23.
Important to identify nodularity. Purely diffuse cases lacking FDC or nodularity are not considered NLPHL and are consistent with THRLBCL or transformation to DLBCL.
Epstein Barr virus typically absent in NLPHL, whilst often found in cHL.[4]
Immunophenotype
Immunophenotype of LP cells helps to differentiate it from cHL.
LP cells are positive for B-cell antigens (CD19, CD20, CD22, CD79a), CD45 and BCL6, and lack CD15 and CD30.[4]

LP cells: lymphocyte-predominant cells; cHL: classic Hodgkin lymphoma; NLPHL: nodular lymphocyte-predominant Hodgkin lymphoma; FDC: follicular dendritic cells; THRLBCL: T-cell / histiocyte-rich large B-cell lymphoma; DLBCL: diffuse large B-cell lymphoma.

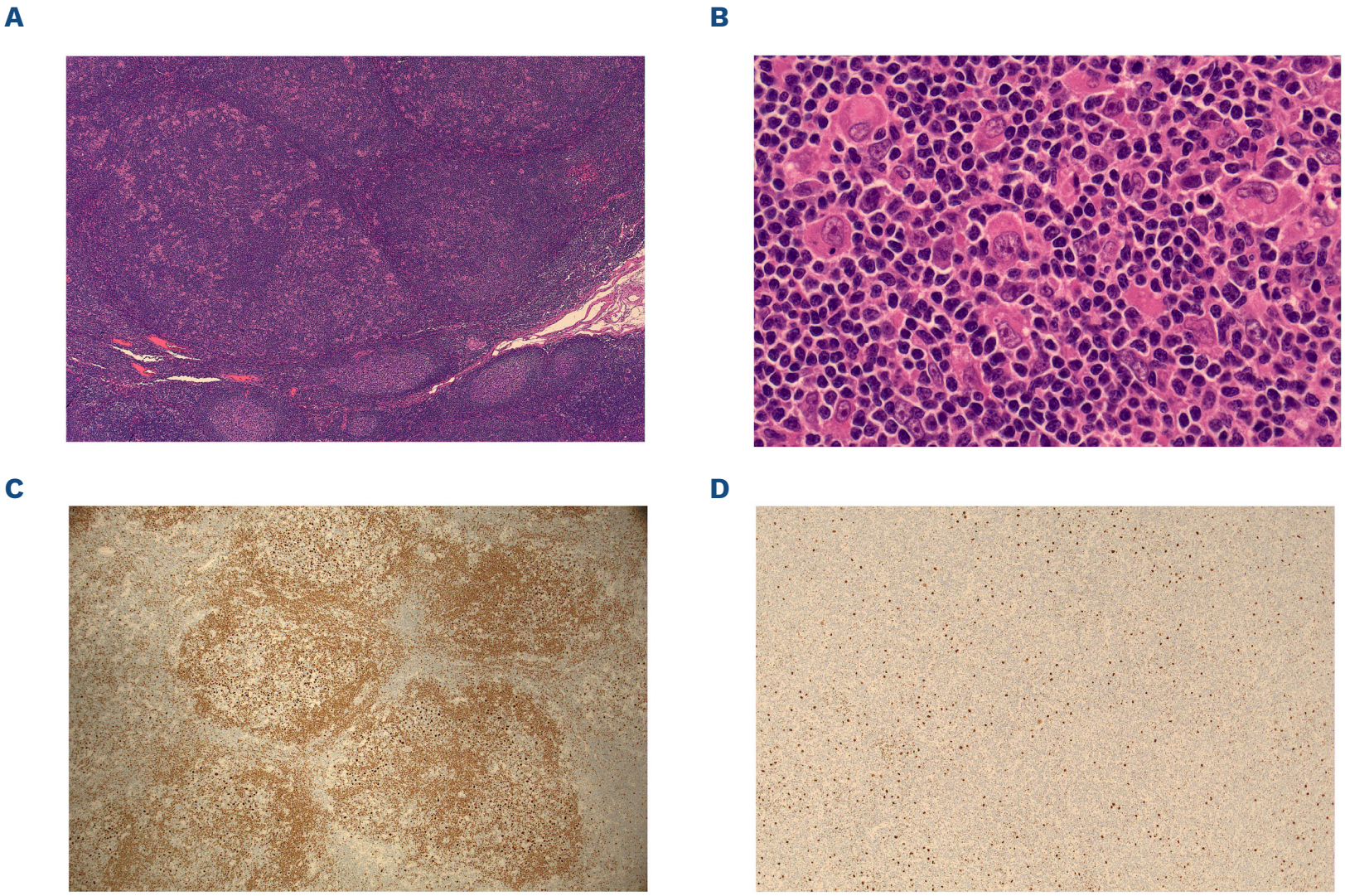

Figure 1. Characteristic histologic images of lymph node sections in patients with nodular lymphocyte-predominant Hodgkin lymphoma. Hematoxylin and eosin stain of a lymph node with partial effacement by nodular lymphocyte-predominant Hodgkin lymphoma, pattern A (B-cell rich nodular), at 5x magnification (A) and at 60x magnification (B) with lymphocyte-predominant (LP) cells peppered among small mature lymphocytes. (C) Immunohistochemistry for OCT2 shows accentuated nuclear staining of LP cells within B-cell rich nodules with weaker staining of small mantle-type B cells. (D) In comparison to (C), OCT2 staining in an area of growth pattern E demonstrates nuclear staining of LP cells diffusely scattered in a milieu composed of predominantly mature T cells and histiocytes.

recently, pattern F has not been grouped with the other variant patterns with more adverse features.

Biology

Efforts have been made to better understand the tumor microenvironment (TME) of patients with NLPHL and its correlation with clinical outcomes.[20] Hartmann and colleagues used immunohistochemistry (IHC) staining to characterize the tumor cells and TME in lymph node samples. In 96% of patients, PD1-positive follicular T-helper cells formed rosettes around tumor cells indicating their important role in NLPHL.

Younes and colleagues analyzed the TME by comparing lymph node biopsies from patients with NLPHL and T-cell / histiocyte-rich large B-cell lymphoma (THRLBCL).[21] Using highplex imaging and spatial profiling at the single cell level, they demonstrated a distinct difference in composition, distribution and interaction of TME B and T cells between typical and variant NLPHL and THRLBCL. This validates the current way of classifying NLPHL and suggests an increased monocyte / macrophage content may distinguish THRLBCL from variant pattern E NLPHL. Beyond the routine staging tests, molecular or genomic testing are currently limited to the research sphere. Molecular testing has identified common mutations in NLPHL tumor cells in signaling pathways such as JAK/STAT.[22] Gene expression profiling via microdissection of tumor cells has demonstrated significant similarity in the genes expressed in both NLPHL and THRLBCL suggesting they are closely related diseases.[23-25] This has been confirmed on comparative genomic hybridization.[26]

Next-generation sequencing (NGS) of immunoglobulin heavy chains (IgH) has been used to characterize the clonal evolution of tumor cells at relapse or transformation to high-grade B-cell NHL.[27] Common features of patients with transformed disease include older age, IgD negativity, higher clonality of both LP cells and background B cells more akin to B-cell NHL, and a lack of the characteristic IgH rearrangement seen in most patients with NLPHL.

Differential diagnosis

Table 2 summarizes the key differential diagnoses and

the differences in morphology, background cells and immunohistochemical stains.

Staging and work-up

In the patient's case history, a key point to note is the presence of constitutional symptoms. Routine blood tests should include lactate dehydrogenase (LDH) and viral serology for hepatitis B and C and human immunodeficiency virus. A bone marrow biopsy is not routinely required due to the low rate of bone marrow involvement and the ability of a positron-emission tomography-computed tomography (PET/CT) scan to sensitively detect bony disease.[28,29]

A PET/CT scan highlights involved lymph nodes and extranodal sites of disease. Bulky disease is defined as a nodal mass of ≥10cm. Staging uses the Ann Arbor staging system whilst patients may be stratified into risk groups as applied by the German Hodgkin Study Group (GHSG).[30] The GHSG uses stage and risk factors such as a large mediastinal mass, extranodal disease, erythrocyte sedimentation rate (ESR), and number of nodal areas to stratify patients into early, intermediate, and advanced stages.

An excisional lymph node biopsy is highly recommended over a core biopsy wherever possible. A larger tissue sample allows for identification of LP cells and enables sufficient IHC stains to differentiate NLPHL from LRCHL. Also, excluding transformation is important, and differentiating NLPHL, especially pattern E, from THRLBCL may be difficult as nodularity may not always be evident in a small biopsy.

Prognosis

Patients with NLPHL typically have a more favorable prognosis than patients with cHL with the disease usually following an indolent course despite the risk of ongoing relapse and transformation.[16] As most patients present with limited stage disease, limited field radiotherapy leads to survival often comparable to the general population.[9] Large population studies show that stage III-IV disease and older age (>60-70 years) are associated with inferior outcomes.[9,31]

Most patients with NLPHL have excellent long-term survival with a 10-year progression-free survival (PFS) rate of 70-75% and a 10-year overall survival (OS) rate of approximately 90%.[2,32] However, approximately 20% of patients experience relapse at a median time of 3-4 years.[32] Of those who relapse, approximately 20% occur more than ten years from diagnosis.[8] Conversely, up to around 30% of those who relapse do so early within the first 24 months after diagnosis.[32] In the GHSG analysis of patients treated in the HD7 to HD15 trials, these patients had a significantly poorer outcome with a 10-year OS of 47.1% compared to 95.9% in those who relapse more than 24 months after initial diagnosis.[32]

Risk stratification of patients is important to optimally balance efficacy and toxicity. Minimizing late effects is vital as the GLOW dataset showed a low 10-year lymphoma-specific death rate of 3.3%.[2] This risk increases for older patients >60 years and in those who experience disease relapse, especially in those who relapse early.[2,32] Treatment-related toxicity, including secondary malignancies, and non-lymphoma deaths outnumber deaths from lymphoma, highlighting the importance of treatment selection.[2,32-35]

Table 2. Differential diagnosis.

	NLPHL	Lymphocyte rich classic Hodgkin lymphoma	T-cell / histiocyte-rich large B-cell lymphoma	Progressive transformation of germinal centers
Clinical features	Approx. 75% limited stage. Painless cervical / inguinal lymphadenopathy. Advanced stage, B symptoms rarer.	Similar presentation to NLPHL. Often early-stage, lacks B symptoms, non-bulky disease.	Majority advanced stage. Approx. 50% B symptoms.	Persistent, asymptomatic lymphadenopathy. Link with autoimmune / chronic inflammatory disorders.
Morphology	Nodular (in part at least). LP cells.	Often nodular; can be diffuse. HRS cells.	Usually diffuse. Malignant cell may resemble LP or HRS cell, immunoblast, centroblast.	≥1 enlarged follicle (3-5x larger than reactive follicle). No LP cells.
Background	Small B lymphocytes, histiocytes, FDC, $PD1^+$ T lymphocytes.	Small lymphocytes.	$CD8^+$ T cells, macrophages, lacks FDC.	Small B cells replace germinal center.
CD20	+	–	+	Not applicable.
CD15	–	+	–	
CD30	–	+	–/+	
CD79a	+	–	+	
CD45	+	–	+	

NLPHL: nodular lymphocyte-predominant Hodgkin lymphoma; LP cells: lymphocyte-predominant cells; FDC: follicular dendritic cells; HRS: Hodgkin/Reed Sternberg; -/+ : minority of cases positive.

The effect of variant IAP on prognosis has recently been challenged. Although analyses from the GHSG (reporting 5-year PFS and relapse rates) and a UK group showed that variant IAP were associated with a worse outcome in both children and adults with NLPHL, longer term follow-up from the GSHG of 86 months did not show any difference in PFS between AB and non-AB patterns.[19,36,37] There was a poorer PFS of statistical significance in patients with patterns D/E.[36] The GLOW Group's dataset of 916 patients with available pathology further challenges the notion that variant IAP is negatively associated with outcome.[2] On multivariant analysis (MVA), there was no association between IAP, PFS, or OS once adjustment for other prognostic factors had been made. However, variant E was linked with a higher risk of transformation to aggressive NHL (hazard ratio [HR], 1.81; $P<0.05$).[2]

A number of groups have developed prognostic scores to risk stratify patients. The GHSG correlated clinical and laboratory results, including IAP pattern, with outcome in 423 patients.[19] A prognostic score was based on factors assessed by MVA including variant IAP, male gender, and low serum albumin (<4 g/dL).[19] This score has not been widely utilized in guidelines to inform treatment choice.

The LP-IPS has been proposed by the GLOW Group who showed on MVA that age ≥45 years, stage III-IV, hemoglobin <10.5 g/dL, and splenic involvement were the most predictive markers of PFS. Higher scores on the LP-IPS correlate with a poorer PFS (HR, 1.52), OS (HR, 2.31), increased transformation (HR, 1.41), and lymphoma-related death (HR, 2.63).[2] In the future, this score may help to guide treatment de-escalation or intensification and inform the design of future prospective trials.

Assessing for relapse and transformation to aggressive non-Hodgkin lymphoma

Patients with NLPHL refractory to initial treatment or those who experience relapse after initial therapy should have a repeat excisional biopsy to re-establish the diagnosis and assess for transformation, most commonly to THRLBCL or to DLBCL. Furthermore, FDG-avid lymph nodes on a PET/CT scan may, in fact, represent reactive lymph nodes including those with progressive transformation of germinal centers. Transformation to aggressive NHL occurs in 2-17% of patients.[38,39] Splenic involvement, variant E IAP, and prior chemotherapy are risk factors for transformation.[40,41] Relapse of NLPHL and disease transformation can

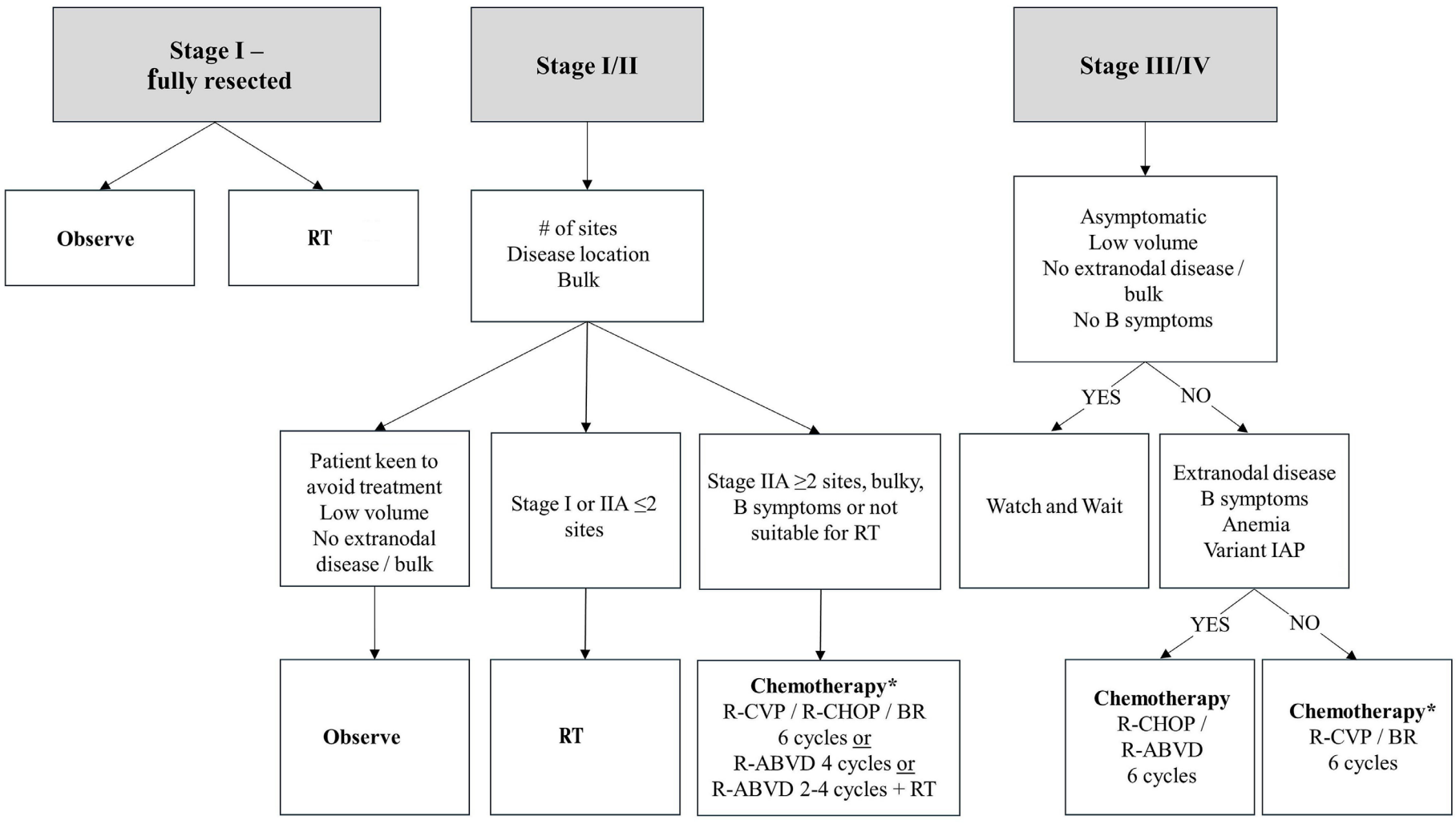

Figure 2. Proposed treatment algorithm. #Number of; R-CVP: rituximab, cyclophosphamide, vincristine, prednisolone; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; BR: bendamustine, rituximab; R-ABVD: rituximab, doxorubicin, bleomycin, vinblastine, dacarbazine, RT: radiotherapy; IAP: immunoarchitectural pattern. *Recommendation that number of cycles of chemotherapy is discussed at a multidisciplinary team (MDT) meeting.

occur many years after the initial diagnosis and long-term follow-up of patients is important.

Management

The treatment algorithm proposed by the authors is shown in Figure 2. It aims to consolidate the current recommendations from various international guidelines and expert groups.

Active surveillance

As patients with NLPHL often follow an indolent course, active surveillance may be considered in select patients with early or advanced stage disease who are asymptomatic and have low tumor bulk. This has been adopted from the approach to low-grade B-cell lymphomas. Despite the lack of randomized data to compare active surveillance with treatment in patients with early-stage NLPHL, results from retrospective analyses suggest that active surveillance is a reasonable strategy for patients unsuitable for RT and in those without extranodal or bulky disease.

A retrospective study by the Lymphoma Study Association included 114 patients (stage I, N=67; stage II, N=37; advanced stage, N=10) who were observed.[42] Of these patients, 65 patients progressed with a median PFS of 56.4 months. At relapse, 8 patients continued with observation alone whilst the remainder received RT, rituximab either alone or with RT, chemotherapy or combined modality treatment (CMT).

A report from the Memorial Sloan Kettering Cancer Center (MSKCC) included 37 patients who underwent active surveillance (early-stage, N=23; advanced-stage, N=14).[43] Only 10 patients (27%) progressed and 9 received treatment at a median time to treatment of 61 months. Bulky disease and extranodal disease were associated with a shorter PFS. Further supporting data come from an analysis of the National Cancer Database, where 68 patients underwent active surveillance with no difference in OS between patients who underwent active surveillance compared to initial treatment (HR, 0.71; *P*=0.41).[44,45]

Fully resected stage I

In adult patients where a single involved lymph node is fully excised, active surveillance is often employed. Treatment with involved-site radiotherapy (ISRT) to reduce the risk of relapse may be considered. A multi-center retrospective analysis by the International Lymphoma Radiation Oncology Group (ILROG) assessed outcomes of patients with stage I to II disease.[33] Of the 32 patients who were observed after excisional biopsy, 25 patients had complete resection without any remaining lymphoma with a 5-year PFS of 79.1%. Patients who were observed, including those without complete excision, had a 5-year OS of 80.8%. In 4 patients initially observed whose lymphoma later relapsed, 3 had advanced stage at relapse.

Treatment of stage I/II disease appropriate for radiotherapy

In patients with early-stage NLPHL, ISRT is an effective treatment strategy that offers equivalent outcomes to chemotherapy or CMT in many patients with stage IA or IIA disease.[33,46-48] However, data from the British Columbia Cancer Agency suggest that apart from patients with stage IA disease, patients with early-stage NLPHL have superior outcomes with CMT compared with RT alone.[49]

There is variation in practice in treating early-stage disease beyond stage IA. The GHSG separates patients with stage IA disease without risk factors, for whom they recommend ISRT, from all other patients with early or intermediate stage disease (stage I/II) for whom they recommend CMT.[30] Stage and risk factors (large mediastinal mass, extranodal disease, elevated ESR or ≥3 nodal areas) are used to categorize patients.[30] This informs the European Society of Medical Oncology's recommendations whilst the National Comprehensive Cancer Network supports ISRT alone for many of these patients.[50,51] Discussing these cases at a multidisciplinary team meeting with hematologists and radiation oncologists is crucial.

In terms of outcomes in patients with early-stage NLPHL, a large retrospective analysis by the ILROG group examined adult patients with stage I or II NLPHL who received all forms of treatment from 1995 to 2018.[33] There were 307 patients with stage I and 252 patients with stage II disease. At five years, the PFS and OS were equivalent in patients who received RT (91.1% and 99.4%) or CMT (90.5% and 99.4%), respectively. These findings mirror the results of a GHSG analysis which looked specifically at patients with stage IA NLPHL and found that, at eight years, PFS and OS were comparable for patients treated with involved-field RT (IFRT) or CMT.[47]

Patients with stage II NLPHL may be suitable for ISRT, but in those with more extensive disease or adverse prognostic features, CMT or chemotherapy alone may be considered. A number of retrospective analyses suggest patients with stage II NLPHL have an inferior PFS compared to patients with stage I.[46,52] In the ILROG analysis, patients with stage II disease and only 2 sites of disease still achieved excellent disease control with RT alone. Conversely, patients with >2 sites of disease had a worse PFS with RT alone. The outcome of CMT was unaffected by number of sites, suggesting patients with >2 sites may benefit from intensification of therapy. For non-contiguous stage II disease, there was no difference on univariate analysis between RT or CMT.

Minimizing the risk of coronary artery disease, lung fibrosis and secondary cancers should be considered when selecting RT as more patients die from complications of therapy

than of lymphoma.[33,46,47] Efforts to minimize toxicity include de-escalation of the radiotherapy field, with ISRT offering equivalent 5-year PFS and OS rates to extended-field or IFRT.[48] The recommended dose of RT is 30 Gray (Gy) in 1.8-2 Gy fractions which has been adopted from the dose used in cHL.[51] In the future, lower doses of RT to further reduce toxicity, such as 4 to 24 Gy, which are very effective in low-grade lymphoma, may be assessed.

Treatment of early disease inappropriate for radiotherapy and advanced stage disease

Anti-CD20 antibody treatment

Rituximab is now commonly incorporated into chemotherapy regimens in patients with NLPHL. Encouraging efficacy of rituximab as monotherapy in the relapsed setting led to its assessment in newly diagnosed patients.[53] A GHSG report details 28 patients with newly diagnosed stage IA NLPHL who received 4 doses of weekly rituximab at 375 mg/m^2.[54] Compared to outcomes offered by more definitive therapies such as RT or CMT, rituximab monotherapy led to a poorer 10-year PFS of only 51.1% but a 10-year OS of 91.1% as patients responded to therapies at relapse.[54] Due to the shorter PFS with rituximab, it is typically not recommended as first-line treatment over RT, chemotherapy or CMT.

Rituximab in patients with advanced stage disease has been investigated in a phase II study that also explored rituximab maintenance in patients with both newly diagnosed and relapsed disease.[40] The rituximab group received 4 weekly doses only whilst the maintenance group received rituximab weekly for four weeks every six months for two years. In patients with newly diagnosed NLPHL (N=21), the 5-year PFS was 41.7% in the rituximab induction alone group and a non-significant increase was seen in the maintenance rituximab group of 51.9%. OS remained excellent despite the relapse rate.

The additive benefit of rituximab to chemotherapy regimens such as ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) or CVP (cyclophosphamide, vincristine, prednisolone) is difficult to quantify due to the lack of randomized trials. However, to limit long-term toxicities from agents such as bleomycin or anthracyclines, rituximab may add efficacy to regimens such as CVP whilst adding minimal toxicity. Retrospective data from the Fondazione Italiana Linfomi (FIL) group suggests adding rituximab to chemotherapy significantly improves PFS in patients with stage II to IV disease compared to chemotherapy alone.[55] The 5-year PFS was 72.7% in patients who received chemotherapy compared to 89.6% in those who received immunochemotherapy. Outcomes with R-ABVD were equivalent to those of R-CHOP.[55]

Chemotherapy

Due to the rarity of NLPHL, there are few prospective trials to guide treatment selection and much of the data is retrospective. There is significant variation in the choice of chemotherapy regimens in patients with both early and advanced stage NLPHL. Table 3 outlines the data supporting various chemotherapy regimens used to treat adults with NLPHL.

Traditionally, regimens for cHL have been used as patients with NLPHL were included in prospective Hodgkin trials.[32] Intensive regimens such as escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) are not typically recommended considering the generally indolent nature of NLPHL, as well as the risk of significant treatment-related toxicities, such as secondary malignancies and increased non-lymphoma deaths.[32]

When CMT is given for early / intermediate stage disease, treatment includes either 2 cycles (for early stage) or 4 cycles (for intermediate stage) of ABVD plus RT resulting in 10-year PFS and OS rates of 79.7% and 93.3%.[32] There are, however, concerns about long-term toxicity from bleomycin, anthracyclines and radiotherapy. Omission of radiotherapy following ABVD results in inferior disease control.[56]

Efforts to reduce treatment in patients with early-stage NLPHL includes using PET to guide therapy. A retrospective report from the British Columbia Cancer Agency (BCCA) included 99 patients, with 63 patients treated in the PET era.[57] After 2 cycles of ABVD, a restaging PET scan was performed (iPET2).[57] PET negative patients had 2 further cycles of ABVD (later changed to AVD like in the RATHL trial) whilst PET positive patients received involved-node RT at 35 Gy.[58] Of 49 patients who underwent iPET2, 82% were PET negative. The 5-year PFS in the PET-adapted group was 92% for PET-negative patients and 80% for PET-positive patients.[57] No relapses occurred in patients with stage II disease who were iPET2 negative and received chemotherapy alone.

Conclusions as to whether chemotherapy alone is as effective as CMT are difficult to make due to the retrospective nature of many analyses. In the ILROG report, a smaller cohort of 47 patients received chemotherapy alone but had a lower 5-year PFS compared to CMT at 77.8% *versus* 90.5%.[33] However, this group included higher risk patients with an increased rate of B symptoms and extranodal disease. Similarly, a retrospective French report by Garciaz *et al*. showed that 4 cycles of R-ABVD achieved a 5-year lymphoma-free survival of 80% in 24 patients (early-stage, N=12).[59]

When treating patients with advanced stage disease, chemotherapy in combination with an anti-CD20 antibody is typically given. Consolidative radiotherapy may be considered where there is concern of persistent lymphoma. Identifying patients at higher risk of relapse or with adverse prognostic markers allows selection of patients who may benefit from anthracycline-containing regimens such as R-CHOP. High-risk features include B symptoms, bulky disease, extranodal involvement (splenic, liver, bone marrow), and mediastinal disease.[31,33,60,61]

As NLPHL is a CD20-positive B-cell lymphoma, in addition to concerns about the ongoing risk of relapse and transformation, R-CHOP has been employed in patients needing systemic therapy either alone or in combination with IFRT. A retrospective analysis from MD Anderson details 27 patients treated with R-CHOP, 11 with early-stage disease, and 16 with advanced stage disease.[62] The 5- and 10-year PFS were 88.5% and 59.3%, respectively. In patients with early-stage disease, there was no difference in PFS between CMT, chemotherapy alone or RT alone but numbers were very small. When patients with advanced stage disease (stage III/IV) were considered alone, the 5- and 10-year PFS were both 85.7%. In comparison to R-CHOP, there are concerns about a possible higher risk of relapse and high-grade transformation in patients with advanced stage disease who receive ABVD.[63] However, the addition of rituximab to ABVD (R-ABVD) showed equivalent outcomes to R-CHOP in the analysis from the FIL group.[55]

Other chemo-immunotherapy regimens including R-CVP and bendamustine-rituximab (BR) have been explored. BR has shown encouraging efficacy but in small numbers of patients.[64,65] In a cohort of 20 patients, with most having advanced stage disease (N=15), the CR rate was 90% with a 68-month PFS rate of 87%.[65] Although data supporting R-CVP are limited, in patients with low-risk disease it offers a balance between toxicity and efficacy.[66] A retrospective analysis from the UK detailed 15 patients treated with CVP; 5 received rituximab, with a 5-year OS of 100%.[66] Notably, data supporting CVP comes mainly from studies in children without rituximab and with vinblastine given rather than vincristine.[67]

Treatment response assessment

The role of interim imaging with PET/CT in patients receiving chemotherapy is unclear as most patients respond to therapy. However, it may play a role in PET-adapted treatment decisions or in the presence of symptoms that are of concern for progression or high-grade transformation. The BCCA report of their PET-adapted approach in patients with limited stage NLPHL showed that RT may be omitted in the majority of patients treated with chemotherapy.[57] However, omission of RT in iPET2-negative limited-stage patients in the BCCA analysis came at the cost of 2 additional cycles of ABVD. Importantly, patients with a negative iPET2 who do not receive additional treatment appear to have an increased relapse rate according to the subgroup analysis of the GHSG HD16 trial.[56]

Treatment of relapsed/refractory nodular lymphocyte-predominant Hodgkin lymphoma

Most patients with NLPHL have a favorable outcome from initial treatment, whilst a smaller proportion relapse, of-

Table 3. Outcomes of chemotherapy regimens in adult patients with nodular lymphocyte-predominant Hodgkin lymphoma.

Chemotherapy	N of patients and stage	Outcomes, %	Key points
ABVD plus RT[32] Early stage: 2 ABVD + RT Intermediate stage: 4 ABVD + RT	471 patients Early: 251 Intermediate: 76	10-year PFS and OS Early: 79.7 + 93.3 Intermediate: 72.1 + 96.2	Prospective trials from GHSG: HD7 to HD15. More deaths due to secondary malignancies than lymphoma-related.
R-ABVD[59] 4 R-ABVD for early stage 6 R-ABVD for advanced stage	24 patients Early: 12 Advanced: 12	5-year PFS: 80 OS not reported	Dacarbazine omitted in 10 patients (i.e., R-ABV). No difference between those who did or did not receive dacarbazine.
BEACOPP-like[32]	220 patients Intermediate: 76 Advanced: 144	10-PFS and OS: Intermediate: 72.1 + 96.2 Advanced: 69.8 + 87.4	Prospective trials from GHSG: HD7 to HD15. Concern about acute toxicity of therapy and risk of malignancies, e.g., AML.
R-CVP[66]	15 patients 5 with rituximab (R-CVP) Early: 11; advanced: 4	PFS: not reported 5-year OS: 100	Cohort included some pediatric patients with age range 12-29.5 years. Median age at diagnosis 16 years.
R-CHOP[62] R-CHOP + IFRT R-CHOP alone	27 patients R-CHOP + IFRT: Early: 6; advanced: 1 R-CHOP alone: Early: 5; advanced: 15	5-year PFS: 88.5 10-year PFS: 59.3	After R-CHOP, only 2 late relapses (6 and 8 years after treatment). Unclear if anthracycline required unless risk factors present.
BR[65]	20 patients Early: 5; advanced: 15	68-month PFS: 87	15 patients were treatment-naïve, 5 patients treated at relapse.

N: number; R-ABVD: rituximab, doxorubicin, bleomycin, vinblastine, dacarbazine; RT: radiotherapy; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone; R-CVP: rituximab, cyclophosphamide, vincristine, prednisolone; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; IFRT: involved-field radiotherapy; BR: bendamustine, rituximab; PFS: progression-free survival; OS: overall survival; EFS: event-free survival; AML: acute myeloid leukemia.

ten multiple times. The majority of those whose disease relapses will respond to further treatment.[34,35] As most patients have an indolent clinical course even at relapse, options include active surveillance, single-agent anti-CD20 monoclonal antibody, radiotherapy or chemotherapy.

For patients with limited stage disease at relapse, RT or chemotherapy with R-CHOP (mindful of lifetime exposure to anthracycline) or R-CVP are options. In patients with advanced stage, options include active surveillance, R-CHOP or R-CVP.

Patients with more aggressive features, such as refractory disease (approx. 1-2% of patients), progression of disease within 24 months (POD24) of initial treatment (in the GHSG analysis after initial treatment up to approx. 30% relapsed early) and liver / bone marrow involvement, have poorer outcomes.[2,32] These patients may benefit from intensive salvage chemotherapy, such as DHAP (dexamethasone, cytarabine and cisplatin), and autologous stem cell transplant (ASCT). In a report by the European Society for Blood and Marrow Transplantation-Lymphoma Working Party, 60 patients with relapsed NLPHL achieved a 5-year PFS and OS of 66% and 87% with salvage chemotherapy and ASCT.[35,68,69]

Treatment of transformation to high-grade B-cell non-Hodgkin lymphoma

Treatment of transformed disease has typically included chemotherapy with rituximab with or without an ASCT. Practice has varied and likely reflects what therapy patients previously received for their NLPHL. In a report from the UK, a cohort of 26 patients with transformed disease had a 5-year PFS of 60% with most receiving ASCT (62%).[70] A French dataset mirrors this finding.[39] In 19 patients who experienced transformation after ABVD, 9 patients had salvage chemotherapy and ASCT whilst 10 patients received conventional chemotherapy. The 10-year OS for all patients was 60%. Whereas in a report by the ILROG group, 21 patients with transformation to DLBCL were mainly treated with R-CHOP (N=15) with only 2 patients receiving ASCT.[33] In this group, the 5-year PFS and OS were 62.2% and 88.4%, respectively. However, these were patients who progressed after more limited treatment for early-stage disease.

As such, patients are either treated with R-CHOP or salvage chemotherapy with ASCT. This choice depends on patient age and comorbidities, whether disease transformation is detected at the time of initial diagnosis or occurs after RT alone, and whether patients have been previously exposed to an anthracycline.

Future directions

Future directions include new ways to genetically characterize patients with NLPHL and whether liquid biopsies, such as peripheral blood, can be used to assess for response. Furthermore, how novel agents may be utilized either in upfront treatment or the relapsed setting is yet to be established.

Circulating tumor DNA (ctDNA) in patients with cHL has been used to more efficiently genotype the lymphoma compared to tumor biopsy material.[71] ctDNA may have the ability to genetically subtype patients based on fragmentation patterns, to predict response to therapy and risk of relapse through measurable residual disease testing.[72] This technology may be applied to patients with NLPHL and could act as a quantifiable, radiation-free biomarker.

There is a paucity of evidence for the use of novel agents in patients with relapsed NLPHL. A recently published phase II study from the GHSG detailed the outcomes of 16 patients with relapsed NLPHL treated with ibrutinib.[73] Patients had disease reassessment with PET/CT after 6 cycles and treatment was continued in those who achieved stable disease or better up to a maximum of 20 cycles. Although the ORR was 67%, the 18-month PFS was only 56.3% with 7 patients progressing or relapsing at a median of ten months.

Other proposed novel agents with a rationale for their use include PD1-directed checkpoint inhibitors due to the rosetting of $PD1^+$ T cells present in the majority of patients. Only one case report details the successful treatment of a patient with relapsed NLPHL who progressed to THRLBCL and achieved a complete response with pembrolizumab.[74] There are only case reports supporting the use of the immunomodulatory agent lenalidomide and these show efficacy in patients with relapsed NLPHL as well as in a patient with transformed disease to THRLBCL who had failed multiple prior lines of therapy.[75-77]

Cellular therapies, including T-cell engaging antibodies such as CD3xCD20 bispecific antibodies or CD19-directed chimeric antigen receptor (CAR) T-cell therapy, may be active in patients with NLPHL.[78] Currently, there is an ongoing phase II trial (clinicaltrials.gov: 05886036) treating patients with newly diagnosed NLPHL with either weekly rituximab or mosunetuzumab, a subcutaneous CD3xCD20 bispecific antibody.

Conclusions

Despite the rarity of NLPHL, growing evidence is helping to stratify patients based upon risk factors, as demonstrated by the LP-IPS. How tools such as the LP-IPS should be used to guide treatment decisions is yet to be clearly established. In most patients, selecting a treatment that minimizes toxicity is crucial as most patients have excellent long-term outcomes. Patients with early-stage disease are generally suitable for IFRT unless there are more than 2 involved sites or those with bulky disease where chemotherapy alone or CMT are recommended. Patients with advanced stage disease may be safely observed if they are asymp-

tomatic, have low-volume disease and lack risk factors. In those with advanced stage disease requiring treatment, identifying patients who may benefit from more intensive anthracycline-containing regimens is important. The choice of treatment for patients with relapsed disease depends on their response to initial therapy, time to relapse, age, and symptoms but most will respond well to further treatment. Intensive salvage chemotherapy and autologous stem cell transplant is reserved for a small number of patients who have experienced multiple relapses with aggressive disease features or those with POD24. The use of novel agents remains largely unexplored due to the rarity of NLPHL but there is hope that agents such as T-cell engaging antibodies and checkpoint inhibitors will offer efficacy.

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Contributions

RTS is responsible for conceptualization, study design, literature search, writing, and the figures. BMA is responsible for the figures, and writing, reviewing and editing the manuscript. GC is responsible for study design, and writing, reviewing and editing the manuscript. CYC is responsible for conceptualization, study design, and writing, reviewing and editing the manuscript.

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