How I Treat

How I treat nodular lymphocyte predominant Hodgkin lymphoma

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Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is an uncommon entity that, in contrast to classical Hodgkin lymphoma (cHL), universally expresses CD20, a hallmark of the disease. The majority of the patients present with early-stage disease, and treatment with local radiation provides excellent disease control and overall survival (OS). For locally extensive or advanced stages, paradigms used for cHL have been employed, with similar outcomes. Unlike cHL, late relapses may occur, as well as a propensity to transform to an aggressive B-cell non-Hodgkin lymphoma that underscores the importance of long-term follow-up and biopsy at the time of relapse. Deaths caused by NLPHL are uncommon, and in older series, secondary malignancies and other treatment-related toxicities contributed appreciably to overall mortality. Expression of CD20 in NLPHL has led to the evaluation of rituximab as a therapeutic option. Although results with single-agent rituximab in the front-line setting are inferior to conventional therapy, rituximab is a reasonable choice for relapsed disease because of the high overall response rate and excellent tolerability. Most patients have a long OS; therefore, overall goals of therapy should be to minimize the risk for relapse and long-term toxicity. (Blood. 2013;122(26):4182-4188)

Introduction

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a unique entity representing ~5% of Hodgkin lymphoma (HL). The largest review defining characteristics was reported by the European Task Force on Lymphoma Project on lymphocyte predominant HL (LPHL) and included data from 426 patients initially diagnosed with LPHL from 17 European and US centers. After expert pathology revision and the availability of immunohistochemistry (IHC), only 219 cases (51%) were confirmed to be LPHL. Therefore, extrapolation of results of earlier studies, performed in an era when stringent IHC criteria were not used, to current management strategies is of limited value.

Pathobiology

An excisional biopsy is essential, along with evaluation by an expert hematopathologist. NLPHL is notable for a distinct malignant cell originally termed lymphocytic and histiocytic and reclassified in the World Health Organization 2008 classification as LP (lymphocyte predominant) cells. Because of their microscopic appearance and increased number of nucleoli, a more descriptive term, “popcorn cells,” has been used. At least 1 nodule containing a mixture of LP cells and small B cells is required for a diagnosis of NLPHL. LP cells are seen in a background of B-cell-rich lymphoid follicles associated with follicular dendritic cell meshworks. Some reports propose the recognition of intrafollicular neoplasia in situ NLPHL, associated with early-stage disease and favorable outcome. Single-cell polymerase chain reaction assays demonstrate clonally rearranged immunoglobulin genes that variably express immunoglobulin mRNA. Different chromosomal abnormalities have been described in two-thirds of cases. Although some genetic lesions have been identified, little is known about the pathogenesis of LP cells. Constitutive activity of nuclear factor κB, Janus kinase/signal transducer and activator of transcription pathway, and BCL-6 transcription factors appear to be involved; however, mutations in the genes coding for nuclear factor κB regulating factors inhibitory nuclear factor κB α and A20 are uncommon. Recently, a germline candidate mutation in the nuclear protein ataxia telangiectasia gene locus has been identified in familial NLPHL.

Immunophenotyping is critical for establishing a diagnosis. Unlike malignant Reed-Sternberg cells in classical HL (cHL), LP cells lack expression of CD15, CD30, and Epstein-Barr virus. A typical B-cell phenotype is seen, and cells express CD20, CD45, CD75, and often, J-chain. Epithelial membrane antigen is present in ~50% of cases. Recently, some cases expressing CD15 have been reported and associated with a more aggressive clinical course. B-cell transcription factors, such as Oct 2a, are overexpressed and are therefore very important diagnostic markers in the search for LP cells in biopsies. A diffuse growth pattern with prominent histiocytes and T cells is seen during the evolution of NLPHL and is often difficult to distinguish from T-cell-rich B-cell lymphoma (TCRBCL). Unlike TCRBCL, the meshwork of follicular dendritic cells and B cells is retained with CD4, CD57, and PD1 rosette-forming T cells. Immunophenotypical and molecular studies demonstrate a LP-cell immunophenotype and a clonal relationship between LP cells and cells of concurrent or subsequent diffuse large B-cell lymphoma (DLBCL), suggesting a common cell of origin. Progressive transformation of germinal centers (PTGCs) can be mistaken for NLPHL. However, its distinction from NLPHL is reliably possible by immunophenotyping, as the transformed germinal centers do not harbor cells expressing the typical immunophenotype of LP cells, and occasionally, PTGC and NLPHL may exist in the same lymph node.

Clinical features

The estimated incidence of NLPHL is ~1.5 per 1 000 000 people per year. In a Finnish registry, the standardized incidence ratio for
NLPHL was 19 (95% confidence interval, 8.8-36) in first-degree relatives compared with 5.3 (95% confidence interval, 3.1-8.4) for cHL, warranting further evaluation of potential genetic and environmental factors. Asymptomatic adenopathy can precede diagnosis by months to years. The largest series is a retrospective analysis by the German Hodgkin Study Group (GHSG) in which 394 patients with NLPHL were compared with 7904 patients with cHL. The median age was 37 years, and 75% of the patients were male. The majority (63%) had early-stage favorable, 16% early-stage unfavorable, and 21% advanced-stage disease. In contrast, more patients with cHL had early unfavorable (39%) or advanced (39%) disease.

In the European Task Force on Lymphoma Project on LPHL, peripheral lymph node sites were most often affected, and in contrast to cHL, significantly fewer patients had B symptoms or extranodal sites of disease. Mediastinal disease was extremely rare, seen only in ~7% of patients. Splenic involvement can be seen and may be associated with occult transformation to an aggressive, large-cell non-HL (NHL). NLPHL is fluorodeoxyglucose (FDG) avid, although the standardized uptake values are generally lower than those observed in cHL. FDG-positron emission tomography (PET) scanning is useful for staging and response assessment in NLPHL; however, the addition of PET imaging has led to alteration of therapy in only ~10% of cases in comparison with use of computed tomography (CT) scanning alone.

Prognostic factors

Early-stage NLPHL has an excellent prognosis. Unfavorable risk factors have been reported as less common in NLPHL than in cHL: 3 nodal areas (28% vs 55%), elevated erythrocyte sedimentation rate (4% vs 45%), extranodal involvement (6% vs 14%), and elevated lactate dehydrogenase (16% vs 32%). A comparison of limited-stage cHL with mediastinal involvement and limited-stage NLPHL showed no overall survival (OS) differences. Similarly, no differences in OS were seen in the GHSG studies between early-stage favorable and unfavorable risk groups of LPHL and cHL. Freedom from treatment failure (FFTF) and OS were worse for patients with advanced-stage disease, hemoglobin levels lower than 10.5 g/dL, or lymphopenia (<8% of white cell count). Age 45 years or older was a negative prognostic factor only for OS. In another study of 88 patients with NLPHL, stage, low albumin, presence of B-symptoms, and poor initial response to treatment were factors associated with an inferior OS. A recent study reported that a peripheral blood absolute lymphocyte count/monocyte ratio of 2 or higher remained as an independent prognostic factor for OS, progression-free survival (PFS), and time to progression after adjusting for International Prognostic Score. If validated, this blood test could potentially be used as a simple biomarker for risk stratification.

Transformation to aggressive NHL

Despite a favorable prognosis, it is recognized that NLPHL can transform into aggressive NHL as late as 2 decades after initial diagnosis. The subtype of DLBCL most frequently seen is TCRBCL. In a French registry-based analysis of pathological rereview of 164 patients diagnosed in 1973-2003, 19 of 66 patients with recurrence presented with histological transformation to an aggressive lymphoma at a median of 4.7 years after initial diagnosis. The OS was inferior compared with those with persistent NLPHL histology at the time of relapse. In a report from the British Columbia Cancer Agency (BCCA), 13 of 95 NLPHL cases experienced transformation into aggressive NHL at a median of 8.1 years. The actuarial risks for transformation were 7%, 15%, and 31% at 10, 15, and 20 years, respectively. Unfavorable risk factors for transformation included splenic involvement (P = .006) and advanced-stage disease (P = .057) at initial diagnosis. As in the previous report, prognosis was worse for patients with transformation than for those with relapsed NLPHL. After treatment with multiagent chemotherapy, followed in many cases by high-dose chemotherapy and autologous stem cell transplantation (ASCT), the 10-year estimates for PFS and OS were 52% and 62%, respectively.

The Stanford group has reported abdominal involvement as a risk factor for transformation. In a study evaluating rituximab as a single agent, 6 patients with abdominal disease at study entry had evidence of transformation at recurrence. Collectively, these transformation rates underscore the importance of long-term follow-up of patients with NLPHL and rebiopsy at the time of relapse.

Therapy

Given the rarity of NLPHL, there are very few prospective studies to guide decision-making. In addition, many of the older series are of limited value, as the diagnosis of NLPHL was made in the pre-IHC era. Although a rationale for management of limited disease with local irradiation alone was proposed in the mid-1980s, in large clinical trials as recently as 2003, NLPHL was not treated differently than cHL. More recently, different treatment algorithms have been used for NLPHL, especially in limited-stage disease. Depending on stage, therapy has consisted of radiation therapy (RT), combined modality therapy (CMT), and chemotherapy alone. The expression of CD20 has added rituximab to the armamentarium of options. Management differs for early versus advanced stages and for frontline versus relapsed disease (Tables 1 and 2).

Treatment of early-stage disease

Radiation therapy

Historically, in the early 1960s, RT management of limited-stage NLPHL was not distinguished from that used for cHL. Treatment evolved from “involved-field” irradiation (IFRT) to “extended-field” (EFRT), “subtotal,” or “total lymphoid” irradiation as the more extensive radiation fields were associated with a superior outcome. However, as NLPHL was identified as a distinct entity, with characteristic presentation, response to therapy, and pattern of relapse, it was also appreciated that excellent outcomes were often achieved with limited RT.

In a retrospective review by the GHSG on the Hodgkin disease (HD)-4 and HD-7 trials, the 2-year FFTF/OS for IFRT versus EFRT was 92%/100% and 100%/94%, respectively. This was an important observation, as more-aggressive initial therapy was associated with greater toxicity and fatality. In fact, in a large European-American retrospective study in which the median follow-up for patients was less than 7 years, 74% of the deaths were a result of causes other than HL. Other retrospective reviews from the United States, as well as Europe, in which patients were treated either with limited or more extensive
irradiation, also failed to show benefit from the extended treatment (Table 1).32-35 However, caution should be taken with attempts to compare results of different studies, given differences in patient selection criteria, staging studies employed, duration of follow-up, and so on.

Most groups that employ primary RT in early-stage disease use the IFRT concept to define radiation fields. The strict definition of IFRT is that the fields conform to the boundaries of the lymphoid regions, as defined for the Ann Arbor classification system.36 In some instances, this definition was modified to exclude the high cervical lymph nodes if only the supraclavicular nodes were involved. More recently, the European Organization for Research and Treatment of Lymphomas (EORTC),38 using the ISRT concept, radiation fields for primary management of NLPHL would include involved nodes, defined by CT and PET, with reasonable extension (~5 cm) after the lymphatic drainage proximally and ~2 to 5 cm distally, depending on regions involved.

RT dose is another variable that has been evaluated only retrospectively. Nearly all series have used doses in the 30- to 40-Gy range, with little evidence of difference in outcome.35 The National Comprehensive Cancer Network (NCCN) recommends a dose of 30 to 36 Gy, and the European Society for Medical Oncology (ESMO) a dose of 30 Gy.39,40 Following up on studies in follicular lymphomas that report high response rates with doses as low as 4 Gy for palliative therapy, a single study of a 4-Gy dose has been reported in NLPHL, yielding a 3-year PFS of only 63%. These results are unacceptable compared with conventional dose therapy and, hence, are not recommended.41

Surgery alone

Observation after surgical resection has been evaluated primarily in pediatric patients. The European Network Group on Pediatric Hodgkin Lymphoma reported on 58 children treated with resection only.42 A total of 51 children (84%) achieved a complete response (CR) after excisional biopsy. The PFS was 57% at 50 months for the entire group, and 67% at 26 months for patients in CR after surgery. All patients with incomplete resection eventually relapsed at a median of 17 months with no effect on OS (100%), suggesting an excellent salvage rate in these patients.

A prospective study by the Children’s Oncology Group reported on 52 patients observed after completely resected stage IA disease. At a median follow-up of 26 months, the 2-year event-free survival and OS were 88% and 100%, respectively.43 In 1 adult study, for which details of patient characteristics are lacking, the

Table 1. Selected studies in stage I to II NLPHL

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Median follow-up, y</th>
<th>Treatment</th>
<th>Outcome (%)</th>
<th>OS (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al, 201034</td>
<td>113</td>
<td>11.3</td>
<td>RT 82%</td>
<td>PFS</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>CMT 12%</td>
<td>Limited RT, 64</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CHT 6%</td>
<td>Regional RT, 84</td>
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<td></td>
<td></td>
<td></td>
<td>10 y</td>
<td>Extended RT, 81</td>
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<td>CHT only, 14</td>
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<td></td>
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<td>CMT only, 83</td>
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<tr>
<td>Nogova et al, 200532</td>
<td>131</td>
<td>3.6</td>
<td>RT 69%</td>
<td>FFTF</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CMT 31%</td>
<td>EFRT, 100</td>
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<td></td>
<td></td>
<td></td>
<td>2 y</td>
<td>IFRT, 92</td>
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<td></td>
<td></td>
<td>CMT, 97</td>
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</tr>
<tr>
<td>Feugier et al, 200423</td>
<td>42</td>
<td>NA</td>
<td>CMT</td>
<td>FFP</td>
<td>80</td>
<td>86</td>
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<td></td>
<td></td>
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<td>15 y</td>
<td>RT, 77</td>
<td>90</td>
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<td>CMT, 68</td>
<td>100</td>
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<tr>
<td>Wirth et al, 200535</td>
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<td>15</td>
<td>RT</td>
<td>FFP</td>
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<td>83</td>
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<td>CMT, 93</td>
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<td>Savage et al, 201145</td>
<td>51</td>
<td>5.7</td>
<td>CHT</td>
<td>FFTF</td>
<td>75.4</td>
<td>100</td>
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<td></td>
<td>10 y</td>
<td>RT</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Shankar et al, 201246</td>
<td>55</td>
<td>3.3</td>
<td>CHT</td>
<td>FFTF</td>
<td>75.4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.3 y</td>
<td>RT</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Mauz-Korholtz et al, 200732</td>
<td>58</td>
<td>3.6</td>
<td>Excision</td>
<td>PFS</td>
<td>57</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.2 y</td>
<td>RT</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

CHT, chemotherapy; NA, not reported/not available.

Table 2. Selected studies in stage III to IV NLPHL

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Median follow-up, y</th>
<th>Treatment</th>
<th>Outcome (%)</th>
<th>OS (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diehl et al, 19991</td>
<td>44</td>
<td>6.8</td>
<td>CHT or CMT*</td>
<td>8 y</td>
<td>FFTF</td>
<td>Stage III, 62</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Stage IV, 24</td>
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<tr>
<td>Nogova et al, 200819</td>
<td>83</td>
<td>4.2</td>
<td>CMT†</td>
<td>4.2 y</td>
<td>FFP</td>
<td>77</td>
</tr>
<tr>
<td>Canellos et al, 201020</td>
<td>37</td>
<td>NA</td>
<td>32%, ABVD or EVA</td>
<td>Failure</td>
<td>75</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>68%, MOPP +/ABVD</td>
<td>“Failure”</td>
<td>32</td>
<td>NA</td>
</tr>
<tr>
<td>Fanale et al, 201021</td>
<td>12</td>
<td>3.5</td>
<td>RCHOP +/-IFRT</td>
<td>5 y</td>
<td>PFS</td>
<td>95</td>
</tr>
<tr>
<td>Xing et al, 201249</td>
<td>42</td>
<td>10</td>
<td>83%, ABVD</td>
<td>FFTF</td>
<td>76</td>
<td>86</td>
</tr>
</tbody>
</table>

ABVD, Adriamycin, Bleomycin, Vinblastine, and dacarbazine; BEACOPP, Bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; DSS, disease-specific survival; EVA, etoposide, vinblastine, and Adriamycin; IMEP, ifosfamide and methotrexate, etoposide, and prednisone; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone; NA, not reported/not available; RCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

*CHT, chemotherapy; MOPP-, ABVD-, or MOPPABVD-like.
†CMT, radiotherapy and COPP/ABV (doxorubicin, bleomycin, and vincristine)/IMEP, COPP/ABVD, or BEACOPP.
BCCA results are provocative, it is important to note that the follow-up ABVD alone if an interim PET scan were normal. Although these (median follow-up, patients ultimately develop disease progression. be recommended routinely in clinical practice, as most of these stage I disease in CR after surgical resection, but this policy cannot observation might be an option in carefully selected patients with patients relapsed, which is a higher percentage than would be similar to that seen by the GHSG. Cumulatively, these studies showed an improvement at 10 years in both PFS and OS, using bleomycin, vinblastine, and dacarbazine with or without RT stages. The higher dose range is restricted to sites of bulkier treatment with CMT and, therefore, is too restrictive for treatment with RT alone. The dose we use is 30 to 36 Gy in 1.5- to 1.8-Gy fractions. The higher dose range is restricted to sites of bulkier disease or disease that regresses very slowly. We do not incorporate chemotherapy or rituximab in the routine management of patients with stage IA to IIA disease.

Recommendations for early-stage disease

Although some centers advocate the use of CMT for patients with stage IA disease, both the NCCN and ESMO recommend IFRT alone. For stage IIA disease, IFRT remains the recommendation from NCCN, whereas the ESMO guidelines recommend CMT, which is analogous to cHL. Neither organization recommends the use of rituximab, either alone or in combination (Table 3). At Stanford, patients with clinical stage I to IIA are managed primarily with RT. Because bone marrow involvement is rare, a biopsy is warranted only in patients with advanced-stage disease, B symptoms, or cytopenias. Patients undergo a thorough imaging evaluation, including a diagnostic CT scan and an FDG-PET scan. To delineate the radiation fields, findings from the physical exam are integrated with the imaging results to define the gross tumor volume, which includes palpably enlarged nodes, enlarged nodes on CT, and PET-positive normal size nodes. The clinical target volume is defined by expanding the gross tumor volume ~1 cm in axial dimensions and 2.5 cm proximally and distally, following the normal anatomy of the lymph node regions but not including normal structures such as muscle and bone. An additional 0.5-cm expansion is incorporated to define the planning target volume. This results in what has been designated ISRT by the International Lymphoma Radiation Oncology Group, a definition that is generally less than classical “involved-field irradiation” and greater than INRT. This is warranted, as the INRT definition was developed primarily for treatment with CMT and, therefore, is too restrictive for treatment with RT alone. The dose we use is 30 to 36 Gy in 1.5- to 1.8-Gy fractions. The higher dose range is restricted to sites of bulkier disease or disease that regresses very slowly. We do not incorporate chemotherapy or rituximab in the routine management of patients with stage IA to IIA disease.

Stage IB to IIB and stage I to II disease with more than 3 sites of involvement or bulky (>10 cm) disease are uncommon presentations for NLPHL and are treated according to protocols used for cHL with similar outcomes (Table 3). Rituximab may be included as a component of systemic therapy, although evidence for an improved outcome is lacking.

Treatment of advanced stages

Advanced-stage presentations of NLPHL occur in 20% to 25% patients. Careful consideration needs to be given to clinical history and sites of disease, as there may be occult transformation.

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Table 3. NCCN and ESMO guidelines for NLPHL

<table>
<thead>
<tr>
<th>Guideline</th>
<th>IA, no risk factors</th>
<th>IB</th>
<th>IIA</th>
<th>IIB</th>
<th>III/IV A</th>
<th>III/IV B</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCN guidelines, version 2.2013 (all category 2A unless otherwise indicated)</td>
<td>Observe* or rituximab</td>
<td>ChT</td>
<td>ChT</td>
<td>ChT</td>
<td>ChT</td>
<td>ChT</td>
</tr>
<tr>
<td>ESMO</td>
<td>IFRT</td>
<td>ChT</td>
<td>ChT</td>
<td>ChT</td>
<td>ChT</td>
<td>ChT</td>
</tr>
</tbody>
</table>

Notes:
- CHT, chemotherapy (for details see reference).
- *Option for completely excised solitary lymph node
- †Category 2B
- ‡Palliation only

10-year PFS was 41%. Collectively, these data suggest that observation might be an option in carefully selected patients with stage I disease in CR after surgical resection, but this policy cannot be recommended routinely in clinical practice, as most of these patients ultimately develop disease progression.

Combined modality therapy

During the last 2 decades, although the standard of care for early-stage cHL has become CMT, there is a paucity of studies comparing CMT with RT alone in early-stage NLPHL.

Retrospective studies from the MD Anderson Cancer Center (MDACC), the GHSG, and the Harvard study groups failed to show improvement in outcome with CMT compared with RT alone (Table 1). In contrast, a retrospective study from the BCBA comparing the outcome of 35 patients treated with RT alone with 51 patients treated with chemotherapy (usually ABVD [adriamycin, bleomycin, vinblastine, and dacarbazine]) with or without RT showed an improvement at 10 years in both PFS and OS, using a chemotherapy-based approach. As with all the retrospective studies noted earlier, cautious interpretation is required because of different selection criteria, variable staging procedures, availability of supportive care, and substantial differences in duration of follow-up for the different therapies.

Chemotherapy alone

There are few data regarding use of chemotherapy alone in adults with early-stage NLPHL (Table 1). Limited pediatric data have used cyclophosphamide, vinblastine, and prednisone and cyclophosphamide, vincristine, procarbazine, prednisone (COPP/ABVD). Although survival was excellent, treatment failure was common. In a retrospective report from the BCBA, no relapses were identified (median follow-up, 3 to 5 years) in a subset of 14 patients treated with ABVD alone if an interim PET scan were normal. Although these BCBA results are provocative, it is important to note that the follow-up is rather brief for this disease, which is often associated with late relapse.

Rituximab in early-stage disease

Because consistent CD20 expression represents a hallmark of NLPHL, prospective studies have evaluated the role of the anti-CD20 antibody rituximab. In a GHSG study, 28 patients with stage IA disease without clinical risk factors received 4 weekly standard doses (375 mg/m²) of rituximab. The overall response rate (ORR) was 100%. However, at a median follow-up of 43 months, 25% of patients relapsed, which is a higher percentage than would be expected after RT alone. In a study from Stanford, 13 previously untreated patients with early-stage NLPHL received rituximab as single agent. Although the response rate was 100%, the relapse rate was similar to that seen by the GHSG. Cumulatively, these studies suggest that although rituximab as a single agent may have a role in the management of NLPHL, it cannot be recommended as a first-line therapy for patients with newly diagnosed, early-stage disease.
Chemotherapy is the mainstay of treatment of patients with advanced stage with regimens similar to those used for cHL (Table 2). Most data are retrospective and include studies conducted across several decades. The BCCA reported a matched control outcome analysis of patients with NLPHL (n = 42) or cHL (n = 82) treated with ABVD or ABVD-like chemotherapy.49 At 15 years, there was a trend toward superior PFS for chL compared with LPHL (72% vs 44%; P = .096). The largest series of patients with advanced disease is from the GHSG, comparing outcomes of 83 patients with NLPHL with outcomes of 3083 patients with cHL included in prospective trials.19 There were no significant differences in 50-month FFTF rates for patients with NLPHL or chL (77% and 75%, respectively; P = .46). Of note, chemotherapy used in the GHSG trials included COPP, COPP/ABVD, COPP/ABV (doxorubicin, bleomycin, and vincristine)/IMEP (ifosphamide, methotrexate, etoposide, and prednisone), and BEACOPP (bleo-
mycin, etoposide, Adriamycin, cyclophosphamide, vincristine, pro-
carbazine, and prednisone) (baseline and escalated) that contain significantly higher doses of alkylating agents than ABVD.

The idea that alkylator-based therapy may have an advantage over non-alkylator-based regimens in NLPHL is also supported by a retrospective analysis from the Cancer and Leukemia Group B of 37 patients with advanced NLPHL.50 Patients were treated with MOPP (mechlorethamine, vincristine, procarbazine, prednisone), MOPP/ABVD, or ABVD/EVA (etoposide, vinblastine, Adriamycin). The relapse rate was 75% among patients treated with ABVD/ EVA but only 32% in patients treated with MOPP or MOPP/ ABVD, suggesting that alkylator-based chemotherapy may be more effective for the treatment of advanced-stage NLPHL. There are also retrospective data on the use of RCHOP (rituximab, cyclo-
phosphamide, Adriamycin, vincristine, prednisone) in advanced NLPHL from the MDACC.51 At a median follow-up of 42 months, no relapse or transformation was seen among 15 patients, again supporting the role of alkylator-based therapy.

The use of rituximab as single agent has also been evaluated in front-line therapy in advanced-stage disease. Despite a high response rate, relapses are common, limiting this option to a palliative setting.29 RT may also serve a palliative benefit in advanced disease.

Recommendations for advanced-stage disease

The NCCN guidelines include a broad range of options that depend on the goals of therapy.39 Curative management generally includes both chemotherapy and rituximab, whereas palliative management includes observation or local radiation. The ESMO guidelines consider management to be the same as for cHL (Table 3).40

At Stanford, patients with advanced disease are treated with curative intent. Given the universal expression of CD20, our usual first-line approach incorporates rituximab with regimens used for cHL. For patients who present with B symptoms or abdominal involvement, scenarios in which there may be occult transformation, we favor using RCHOP for 6 cycles.51

Treatment of relapsed NLPHL

Patients with NLPHL, in comparison with those with cHL, have an increased risk for late relapse for which standard treatment is not well-defined.19,28,53 A subset may develop chronic relapsing disease, with new manifestations of disease appearing during a period of many years, often with limited extent in peripheral nodes. Palliative management is appropriate for this group. Therapy decisions depend on multiple factors, including prior therapy response duration, treatment intent, and comorbidities. Biopsy documentation of clinical relapse is essential to exclude PTGC or transformation to an aggressive B-cell lymphoma.

Unlike relapsed cHL, data on high-dose chemotherapy followed by ASCT for relapsed NLPHL are scarce and largely based on retrospective series. The MDACC reported on 26 patients with relapsed NLPHL treated with high-dose chemotherapy and ASCT between 1990 and 2008. With a median follow-up of 50 months, the 5-year OS and EFS were 76% and 69%, respectively.54 In another study, outcomes with ASCT of 19 patients with relapsed or refractory NLPHL were compared with those of 299 patients with relapsed/refractory cHL. The 5-year PFS and OS were similar, at 50% vs 39% (P = .30) and 56% vs 53% (P = .36), respectively.55

Other treatment modalities, such as localized RT, conventional chemotherapy, or CMT, may also be options, although no large series on these strategies has been published to date. Case reports with rituximab plus ifosfamide, carboplatin, and etoposide (RICE) suggest a high ORR, but durability is unknown.56

Prospective studies have evaluated the role of rituximab in the relapsed setting. At Stanford, a phase 2 study included 18 patients with relapsed NLPHL treated with 4 weekly doses of rituximab (R alone) at standard doses (n = 11) or R + R maintenance (MR) for 2 years (n = 7). At the end of induction therapy with R, ORR was 100% (CR, 78%).29 Although the estimated 5-year PFS of the patients treated with R + MR was 71.4% (95% CI, 44.7-100), it was not statistically significantly superior to R alone (5 year PFS, 36.4%; 95% CI, 16.6-79.5), likely as a result of small patient numbers. The median OS was not reached for either group. In a study conducted by the GHSG, 15 patients with relapsed NLPHL received 4 weekly standard doses of rituximab. All but 1 patient responded to treatment. After a median observation of 63 months, the median time to progression was 33 months, and median OS not reached.57 Cumulatively, these data suggest that although treatment with rituximab alone results in an excellent initial response, therapy is not curative, and a continuous pattern of relapse is seen, despite MR. However, given the excellent tolerability of rituximab, monotherapy use in the relapsed setting is a reasonable consideration.

Recommendations for relapsed disease

The NCCN guidelines emphasize the importance of rebiopsy. Patients who relapse with transformation should be managed according to algorithms for DLBCL. Symptomatic patients with a documented relapse of NLPHL may be treated with any combination of chemotherapy, rituximab, or RT, depending on the extent of disease and nature of the symptoms. Asymptomatic patients may also be observed.39

At Stanford, we follow NCCN guidelines, and selection of salvage therapy depends on treatment intent and disease burden. For localized relapse, consideration is first given to local radiotherapy. For asymptomatic patients with low tumor burden, we often observe without therapy and use guidelines similar to those used in follicular lymphoma to determine treatment indications.58 Single-agent rituximab is often the first choice considered. For patients who have significant tumor burden and are transplant-eligible, we favor using

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a standard salvage regimen (ie, RICE) for 2 to 3 cycles. For transplant-ineligible patients, palliation with single-agent rituximab is preferred.

**Conclusions**

NLPHL is rare, with few prospective trials to guide therapy. RT continues to play an integral role in stage I to II disease, as does chemotherapy in advanced stages. The optimal chemotherapy is debatable, and some data suggest that including an alkylating agent may improve efficacy. Although the results with single-agent rituximab in the front-line setting are inferior to conventional therapy, rituximab is a reasonable choice for patients with relapsed disease. The inherent risk of developing an aggressive B-cell lymphoma underscores the importance of long-term follow-up, as well as rebiopsy at relapse. Randomized trials are likely not feasible because of the rarity of NLPHL; however, strategies to consider testing include “watch and wait” for selected patients, such as young children with limited asymptomatic disease or individuals with totally excised solitary nodal involvement, and combinations of targeted therapy, such as rituximab or other anti-CD20 monoclonal antibodies with conventional therapy. The ultimate goal must be maintenance of excellent PFS and minimization of risk for late effects.

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**References**


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