



## Nodular lymphocyte-predominant Hodgkin lymphoma: a unique disease deserving unique management

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Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare lymphoma entity with an incidence of 0.1 to 0.2/100 000/y. Compared with the more common subtypes of classical Hodgkin lymphoma, NLPHL is characterized by distinct pathological and clinical features. Histologically, the disease-defining lymphocyte predominant cells consistently express CD20 but lack CD30. Clinically, NLPHL mostly has a rather indolent course, and patients usually are diagnosed in early stages. The prognosis of early-stage NLPHL is excellent, with progression-free survival and overall survival rates exceeding 90% after involved-field radiotherapy (IF-RT) alone (stage IA) or combined modality treatment consisting of a brief chemotherapy with 2 cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy followed by IF-RT (early stages other than stage IA). In contrast, patients with advanced disease at diagnosis tend to relapse either with NLPHL histology or with histological transformation into aggressive B-cell non-Hodgkin lymphoma despite more aggressive first-line treatment with 6 to 8 cycles of multiagent chemotherapy. However, even NLPHL patients with multiple relapses successfully respond to salvage therapy in many cases. Salvage therapies range from single-agent anti-CD20 antibody treatment to high-dose chemotherapy followed by autologous stem cell transplantation. Treatment at disease recurrence should be chosen on the basis of various factors, including histology at relapse, time to relapse, extent of disease at relapse, and prior treatment. Because death among NLPHL patients is more often caused by therapy-related late effects than lymphoma-related complications, optimizing the risk-benefit ratio of treatment by decreasing toxicity whenever possible is the major goal of clinical research in this disease.

### Learning Objectives

- Review the distinct pathological and clinical characteristics of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)
- Discuss the treatment options for NLPHL

### Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare entity accounting for ~5% of all Hodgkin lymphoma cases; hence, the incidence is 0.1 to 0.2/100 000/y. Treatment for NLPHL traditionally has been similar to classical Hodgkin lymphoma (cHL).<sup>1</sup> However, there is ongoing debate about whether the standard approaches used in cHL should also be considered standard in NLPHL given the distinct pathological and clinical features of NLPHL.

### Pathological characteristics of NLPHL

The presence of lymphocyte predominant (LP) cells is the prerequisite for the diagnosis of NLPHL. LP cells typically are embedded in large nodules of B lymphocytes (growth patterns A and B according to Fan et al<sup>2</sup>), but variants that are characterized by LP cells located outside the nodules, a T-cell-rich nodular growth pattern and T-cell-rich or B-cell-rich diffuse growth patterns, respectively, have also been described (growth patterns C, D, E, and F according to Fan et al). Variant growth

patterns are associated more often with advanced disease and disease recurrence than typical growth patterns.<sup>3</sup> The immunophenotype of the LP cells differs significantly from the malignant Hodgkin and Reed-Sternberg (H-RS) cell in cHL. Of note, the B-cell marker CD20 is consistently found on LP cells but only infrequently expressed on H-RS cells. Conversely, LP cells stain negative for the surface protein CD30, which represents a hallmark of H-RS cells (Table 1).<sup>1</sup> Gene expression profiling analyses have revealed a high similarity between NLPHL and cHL on one hand and T-cell-rich B-cell lymphoma (TCRBCL) on the other.<sup>4,5</sup> The latter finding is supported by the tendency of NLPHL to transform into TCRBCL.<sup>6-8</sup> Thus, NLPHL represents a lymphoma entity with distinct pathological characteristics that should influence treatment decisions in patients diagnosed with this rare disease.

### Treatment of stage IA disease

Although gene expression profiling analyses have shown similarities to cHL and TCRBCL, NLPHL usually has a more indolent clinical course than these entities. The majority of patients are diagnosed in early stages, including a relevant proportion presenting with stage IA.<sup>1</sup> According to the available data, patients with stage IA NLPHL can be treated less aggressively than patients with stage IA cHL without compromising the prognosis.

A total of 113 patients with stage I/II (stage I, 71 patients; stage II, 42 patients) NLPHL were evaluated in a retrospective study from the

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Off-label drug use: Chemotherapy and anti-CD20 antibody treatment in nodular lymphocyte-predominant Hodgkin lymphoma.

**Table 1. Epidemiological, clinical, and histological characteristics of NLPHL and cHL**

	NLPHL	cHL
Incidence	0.1-0.2/100 000/y	2-4/100 000/y
Male/female ratio	3:1	1.3:1
Median age, y	37	33
<b>Stage at diagnosis</b>		
Early, %	63	22
Intermediate, %	16	39
Advanced, %	21	39
<b>Risk factors</b>		
Elevated ESR, %	4	45
≥3 lymph node areas involved, %	28	55
Extranodal disease, %	6	14
Large mediastinal mass, %	31	55
<b>Histological marker</b>		
CD20	+	±
CD30	–	+
CD45	+	–
CD15	–	+
CD79a	+	±

Adapted from Nogová et al<sup>28</sup> with permission. cHL, classical Hodgkin lymphoma; ESR, erythrocyte sedimentation rate; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma.

United States. The median observation time was 136 months. Treatment consisted of radiotherapy (RT) alone, combined modality treatment (CMT), or chemotherapy alone. Progression-free survival (PFS) estimates at 5, 10, and 15 years were 95%, 89%, and 76% for patients with stage I disease receiving RT alone. The corresponding overall survival (OS) rates were 98%, 96%, and 89%. There were no outcome differences between patients receiving extended-field RT (EF-RT), regional field RT, or limited-field RT. The addition of chemotherapy could not improve the treatment results.<sup>9</sup>

A larger retrospective study from the German Hodgkin Study Group (GHSg) included patients with stage IA NLPHL treated with involved-field RT (IF-RT) alone (n = 108), EF-RT alone (n = 49), or CMT (n = 72). The 8-year PFS rates for patients receiving IF-RT, EF-RT, and CMT were 91.9%, 84.3%, and 88.5% and, thus, did not differ. The excellent PFS rates translated into 8-year OS rates close to 100% (IF-RT, 99.0%; EF-RT, 95.7%; CMT, 98.6%).<sup>10</sup>

**Table 2. Definition of risk groups according to the EORTC/LYSA and the GHSg**

Risk group	EORTC/LYSA	GHSg
Early stages	CS I-II without risk factors (supradiaphragmatic)	CS I-II without risk factors
Intermediate stages	CS I-II with ≥1 risk factors (supradiaphragmatic)	CS I, CS IIA with ≥1 risk factors
Advanced stages	CS III-IV	CS IIB with risk factors C/D, but not A/B
Risk factors	(A) large mediastinal mass (B) age ≥50 y (C) elevated ESR (D) ≥4 nodal areas	CS IIB with risk factors A/B, CS III/IV (A) large mediastinal mass (B) extranodal disease (C) elevated ESR (D) ≥3 nodal areas

Elevated ESR is defined as >50 mm/h without B symptoms and >30 mm/h with B symptoms. Large mediastinal mass is defined as more than one third of the maximum horizontal chest diameter. B symptoms are fever, night sweats, and unexplained weight loss of >10% over 6 mo. CS, clinical stage; EORTC, European Organisation for Research and Treatment of Cancer; GHSg, German Hodgkin Study Group; LYSA, Lymphoma Study Association.

Deaths among patients with stage I NLPHL are due to treatment-related late effects rather than to lymphoma-related complications.<sup>9,10</sup> Treatment toxicity, therefore, should be reduced whenever possible.

A small study from the Netherlands and France evaluated IF-RT alone at a dose of only 4 Gy in 9 patients with limited disease at initial diagnosis (n = 3) or disease recurrence (n = 6). The overall response rate (ORR) was 89%. However, after a median follow-up of 37 months, 5 patients had relapsed, so this reduced-intensity approach does not seem to be sufficient.<sup>11</sup>

A phase 2 study investigated the anti-CD20 antibody rituximab administered as a single agent in 28 stage IA patients. All patients responded to treatment, but the relapse rate was higher than that after IF-RT alone.<sup>10,12</sup>

A study from the Children's Oncology Group, which included children and young adults up to the age of 21 years, investigated a surgery-alone approach in patients with stage IA NLPHL without residual disease after lymph node resection. Fifty-two patients had a total resection according to computed tomography and positron emission tomography scans and thus, did not receive RT or chemotherapy. After a median follow-up of 56.3 months among patients without disease recurrence, the 5-year event-free survival estimate was 77.0%. No patient died during the observation period.<sup>13</sup> Given these results, resection alone may represent a treatment option in selected patients with stage IA NLPHL. However, data on resection-only approaches in adult patients are pending; therefore, whether the results from the Children's Oncology Group study can be translated to older patients is unclear.

Taken together, the available data indicate that limited-field RT alone should be the standard approach for the majority of patients with stage IA NLPHL. The commonly used radiation dose is 30 Gy. The question of whether a moderate dose reduction is possible without a loss of efficacy is unanswered to date. With regard to the radiation field, the current guidelines from the International Lymphoma Radiation Oncology Group (ILROG) recommend involved-site RT (IS-RT), although most available data are on IF-RT.<sup>14</sup> Alternative approaches, such as anti-CD20 antibody treatment, conventional chemotherapy, and resection only, should be discussed in patients with contraindications to RT.

### Treatment of early stages other than stage IA and intermediate stages

In NLPHL, the treatment of early stages other than stage IA and intermediate stages (Table 2) usually consists of CMT and thus, is

similar to that of cHL. A study that used the British Columbia Cancer Agency database compared the outcome of early-stage NLPHL patients treated with RT alone ( $n = 32$ ) between 1966 and 1993 and patients treated with 2 cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or ABVD-like chemotherapy followed by RT or with ABVD chemotherapy alone ( $n = 56$ ) between 1993 and 2009. After a median follow-up of 6.4 years for all 88 patients included in the analysis, the 10-year PFS estimate was significantly better for patients who received chemotherapy-containing treatment than for patients treated with RT alone (91% vs 65%;  $P = .0024$ ). The OS did not differ significantly between the patient groups.<sup>15</sup>

A recent analysis from the GHSG including 271 patients with early-stage NLPHL treated within the HD7, HD10, and HD13 trials also supported the use of CMT consisting of ABVD-based chemotherapy followed by limited-field RT. At 8 years, PFS and OS rates after 2 or 4 cycles of chemotherapy plus RT were 83.2% and 95.1%, respectively.<sup>16</sup>

In patients with contraindications against the use of anthracyclines, the CVP (cyclophosphamide, vinblastine, prednisolone) protocol may represent an alternative. An analysis of 45 pediatric patients with early-stage NLPHL who had received 3 cycles of this regimen as first-line treatment demonstrated a complete remission rate of 80%. At 40 months, 12 of 45 patients developed an event resulting in a freedom from treatment failure (FFTF) rate of 75.4%; 9 patients had not achieved complete remission as a treatment outcome at the end of CVP chemotherapy and thus had received either additional chemotherapy or RT, and 3 patients had disease recurrence and underwent conventional salvage chemotherapy. The OS rate was 100%.<sup>17</sup> However, whether these results from children with NLPHL can be translated to adult patients is unclear, so the use of CVP should be restricted to patients not eligible for ABVD chemotherapy.

Taken together, a brief chemotherapy with 2 cycles of ABVD followed by consolidating RT represents the treatment of choice in early-stage NLPHL, except for stage IA. On the basis of the results from the randomized GHSG HD10 study that included 81 NLPHL patients, a radiation dose of 20 Gy is likely sufficient.<sup>18</sup> In terms of the radiation field, the current ILROG guidelines recommend consolidating IS-RT, although most of the available data are on IF-RT.<sup>14</sup>

Only few NLPHL patients present with intermediate-stage disease. These patients usually are treated with the same approaches used to treat cHL (eg, 4 cycles of ABVD followed by consolidating RT). The commonly used radiation dose is 30 Gy. With regard to the radiation field, the ILROG guidelines also recommend IS-RT in this patient group.<sup>14</sup> The treatment of NLPHL patients in early and intermediate stages may be optimized by the partial replacement of conventional chemotherapy by anti-CD20 antibodies and the reduction of RT fields and doses.

### Treatment of advanced stages

Several analyses that addressed the outcome of patients with advanced NLPHL (Table 2) have become available in recent years. Both cHL approaches, such as ABVD or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), and the standard B-cell non-Hodgkin lymphoma (B-NHL) protocol R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) were evaluated.

A matched-pair analysis that used the British Columbia Cancer Agency database included 42 patients with advanced NLPHL and 84

patients with cHL. Treatment consisted of chemotherapy with ABVD or ABVD-like regimens. After a median follow-up of 11.3 years for NLPHL patients and 10.7 years for cHL patients, the 10-year FFTF and OS rates were comparable for both groups. However, the definition of FFTF did not include cases of lymphoma recurrence with histological transformation. Those cases were taken into account in the definition of time to progression (TTP). As a result, the TTP was significantly impaired ( $P = .04$ ) in patients initially diagnosed with an NLPHL histology because the patients had a cumulative 15-year transformation risk of 24%.<sup>19</sup>

A similar analysis was conducted by the Princess Margaret Cancer Center in Toronto, Ontario, Canada. Forty-seven NLPHL patients were matched with 126 cHL patients. However, only 8 of the NLPHL patients and 18 of the cHL patients had stage III/IV disease. All patients were treated with ABVD chemotherapy. Despite small patient numbers, there was a trend toward a poorer 5-year disease-free survival in patients with NLPHL histology.<sup>20</sup> On the basis of the results from the 2 Canadian analyses, ABVD does not appear to represent the optimal chemotherapy protocol for advanced NLPHL.

The R-CHOP regimen has increasingly been used in the treatment of advanced NLPHL. The largest report on the use of this protocol so far has come from the MD Anderson Cancer Center. Fourteen patients with advanced NLPHL who had been treated with R-CHOP with the option to follow with RT were included in a retrospective analysis. All patients responded to treatment. The 5-year PFS rate was 85.7%. No NLPHL-related deaths and no cases of histological transformations were observed after a median follow-up of 6.6 years.<sup>21</sup>

The more aggressive BEACOPP regimen also showed better treatment results than ABVD. An analysis from the GHSG including 144 patients with advanced NLPHL who had received therapy within the HD9, HD12, and HD15 trials revealed 8-year PFS and OS rates of 76.2% and 87.4%, respectively.<sup>16</sup> However, given the mostly limited tumor burden even in patients with advanced NLPHL, a relevant proportion of this patient group likely was overtreated with the current GHSG standard of care for advanced cHL consisting of 6 cycles of escalated BEACOPP.

Despite limited available data, R-CHOP appears to represent the treatment approach with the most favorable risk-benefit ratio for patients with advanced NLPHL. Only selected patients presenting with poor-risk features, such as large lymphoma masses, extranodal disease, or bone marrow involvement, may benefit from more aggressive BEACOPP-based treatment.

### Treatment of relapsed NLPHL

In patients with histologically confirmed recurrence of NLPHL, different treatment approaches, including single-agent anti-CD20 antibody treatment, conventional chemotherapy, optionally followed by RT and high-dose chemotherapy followed by autologous stem cell transplantation (ASCT), have been shown to be active. Prospective studies were conducted with the anti-CD20 antibodies rituximab and ofatumumab. A small phase 2 study by the GHSG included 15 patients treated with 4 weekly doses of rituximab at a dose of 375 mg/m<sup>2</sup>. The ORR was 94%. After a median follow-up of 63 months, the median TTP was 33 months. Only 1 patient died during the observation period.<sup>22</sup> The ORR among relapsed NLPHL patients treated with 4 weekly infusions of rituximab alone ( $n = 11$ ) or rituximab induction followed by rituximab maintenance every 6 months for 2 years ( $n = 7$ ) within a phase 2 study from the United States was 100%. The 5-year PFS and OS estimates were 36.4% and 90.0%, respectively, after 4 weekly rituximab infusions alone and

71.4% and 71.4% after rituximab induction followed by rituximab maintenance.<sup>23</sup> A phase 2 study that investigated the second-generation anti-CD20 antibody ofatumumab in relapsed NLPHL patients showed an ORR of 96%. After a median follow-up of 26 months, the 1-year and 2-year PFS estimates were 93% and 80%. No patient died during the observation period.<sup>24</sup> Thus, single-agent anti-CD20 antibody treatment results in an ORR close to 100% as well as in sustained responses in a relevant proportion of patients with relapsed NLPHL.

A recent analysis reported that in 99 NLPHL patients who had received first-line treatment within GHSG studies and had developed disease recurrence with NLPHL histology during follow-up, salvage treatment consisted of conventional chemotherapy optionally followed by RT in 32%, anti-CD20 antibody treatment either alone or in combination with conventional chemotherapy in 26%, and high-dose chemotherapy followed by ASCT in 28%. In 13% of these patients, either salvage treatment was unknown (9%) or no therapy was applied at relapse (4%). With a median observation of 3.8 years after disease recurrence, the 5-year PFS and OS estimates were 78.6% and 88.2%, respectively, after conventional chemotherapy optionally followed by RT, 72.4% and 100% after anti-CD20 antibody treatment either alone or in combination with conventional chemotherapy, and 90.0% and 96.0% after high-dose chemotherapy followed by ASCT. Of note, patients who had initially been treated for early-stage disease were more often treated with conventional chemotherapy optionally followed by RT or with anti-CD20 antibody either alone or in combination with conventional chemotherapy. In contrast, patients with advanced-stage disease at initial diagnosis more frequently received high-dose chemotherapy followed by ASCT as salvage therapy.<sup>25</sup>

High-dose chemotherapy followed by ASCT also has been investigated in several other retrospective studies. The largest analysis is from the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. Fifty-six patients who had histologically confirmed NLPHL at relapse were included. Most presented with adverse characteristics, such as stage III/IV disease or B symptoms, and the median time from initial diagnosis to salvage treatment with high-dose chemotherapy followed by ASCT was only 21 months. After a median follow-up of 5 years, the 5-year PFS and OS rates in this poor-risk patient group were 67% and 86%, respectively.<sup>26</sup> These results are consistent with those of other studies that evaluated high-dose chemotherapy followed by ASCT in relapsed NLPHL, such as a report from the MD Anderson Cancer Center of 18 patients who had 5-year event-free survival and OS rates of 61% and 73%, respectively, after high-dose chemotherapy followed by ASCT.<sup>27</sup>

In summary, the choice of salvage treatment in relapsed NLPHL should be made individually. Factors such as time to relapse, tumor burden at relapse, and previous treatment should be taken into account. In contrast to cHL, high-dose chemotherapy followed by ASCT does not represent the standard of care in this situation and is only necessary in the minority of NLPHL patients with disease recurrence.

### Treatment of histological transformation into aggressive B-NHL

Unlike cHL, transformation into aggressive B-NHL occurs in a relevant proportion of NLPHL patients, especially those who initially present with splenic involvement. The 10-year transformation rate is about

**Table 3. Summary of recommendations for newly diagnosed NLPHL**

Stage	Treatment
Stage IA	30-Gy IS-RT alone
Early stages except for stage IA	2 × (R-)ABVD + 20-Gy IS-RT
Intermediate stages	4 × (R-)ABVD + 30-Gy IF-RT
Advanced stages	6 × R-CHOP ± localized RT at 30 Gy

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; IF-RT, involved-field radiotherapy; IS-RT, involved-site radiotherapy; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RT, radiotherapy.

10%.<sup>6-8</sup> Thus, a biopsy specimen should be obtained in all patients with suspected NLPHL relapse to exclude histological transformation.

There is no standard treatment for NLPHL patients who relapse with histological transformation into aggressive B-NHL. Patients who had already received chemotherapy as part of their NLPHL treatment usually are candidates for high-dose chemotherapy followed by ASCT. Patients whose NLPHL treatment did not include chemotherapy (eg, those who had RT alone at initial NLPHL diagnosis) may be treated with R-CHOP or other conventional chemotherapy. Of note, most NLPHL patients with histological transformation at disease recurrence respond successfully to salvage treatment. An analysis of 17 patients with transformed NLPHL revealed a 5-year OS rate of 76.4%.<sup>7</sup> According to another report of 13 patients with histological transformation into aggressive B-NHL, the 10-year PFS and OS rates were 52% and 62%, respectively.<sup>6</sup>

### Future directions

As a result of pathological and clinical differences, the treatment of NLPHL differs from cHL in some clinical settings, including stage IA disease, advanced-stage disease (Table 3), and relapsed disease. The question of whether the best treatment of patients with early-stage, except for stage IA, and intermediate-stage disease consists of the standard approaches from cHL is unclear. Because even patients with relapsed NLPHL have a favorable prognosis, treatment associated with a low risk for acute and long-term toxicity should be applied whenever possible. Treatment approaches may include anti-CD20 antibodies alone as well as in combination with conventional chemotherapy or RT. In the future, targeted drugs other than anti-CD20 antibodies could play a role in NLPHL. In this regard, the GHSG currently is conducting a phase 2 study evaluating the Bruton tyrosine kinase inhibitor ibrutinib in patients with relapsed NLPHL ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) #NCT02626884).

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