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Supplement Article

XVIII. Management of nodular lymphocyte predominant Hodgkin lymphoma

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Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) represents only ~5% of Hodgkin lymphoma (~1.5 per 1 000 000 people per year) [1,2]. Microscopically, NLPHL displays a nodular growth pattern, although a diffuse growth pattern with prominent histiocytes and T cells can be seen in advanced or recurrent cases. The malignant cells of NLPHL, referred to as LP or 'popcorn cells' because of their microscopic appearance, express CD20, and immunophenotyping, is critical for establishing the diagnosis. LP cells express B-cell-associated antigens CD20, CD45, and CD79a and often J-chain but lack expression of CD15 and CD30 [3]. Immunophenotypic and molecular studies demonstrate a clonal relationship between LP cells and cells of concurrent or subsequent diffuse large B cell lymphoma, suggesting a common cell of origin. Progressive transformation of germinal centres can be mistaken for NLPHL; however, the transformed germinal centres do not harbour cells expressing the typical immunophenotype of LP cells [3].

Clinical features

Lymphadenopathy may precede the diagnosis by months to years. The median age is 37 years with a male (75%) predominance [1]. The majority of patients are asymptomatic, have early stage favourable disease (63%), and peripheral lymph nodes are most often affected. Mediastinal and extranodal diseases are uncommon [2]. NLPHL is fluorodeoxyglucose avid, and fluorodeoxyglucose–*positron emission tomography* scanning is useful for staging and response assessment [4]. Unfavourable prognostic factors include ≥45 years, presence of B symptoms, advanced stage, haemoglobin <10.5 g/dl, lymphopenia (<8% of white blood cell count), and low albumin [1]. NLPHL may transform into an aggressive B-cell lymphoma, often *T-cell-rich B-cell lymphoma*, as late as 2 decades after initial diagnosis, which underscores the importance of long-term follow-up of patients with NLPHL and re-biopsy at the time of relapse. Ten-year rates of transformation are reported to be 12–15% [5,6]. Factors associated with transformation include splenic involvement, abdominal involvement, and advanced disease at presentation [5–8].

Therapy

There are few studies to guide treatment decisions. In addition, older retrospective series are of limited value because the diagnosis of NLPHL may have been made without confirmation by *immunohistochemistry* [8]. Key studies have been summarized in Tables 1 and 2.

Treatment of early stage disease (Table 1)

Radiation therapy (RT) alone has often been used for stage I–II NLPHL. In a retrospective review of the German Hodgkin Lymphoma Study Group (GHSG) HD-4 and HD-7 trials, the 2-year freedom from treatment failure (FFTF)/overall survival (OS) for involved field radiotherapy, and extended field RT were 92, 100, and 100%, 94% respectively which suggests that limited RT is associated with an excellent outcome. The International Lymphoma Radiation Oncology Group has defined 'involved site' radiotherapy (ISRT) for Hodgkin lymphoma [8,9]. Using the ISRT concept, radiation fields for stages I–II NLPHL include involved nodes, defined by positron emission tomography–computed tomography, with reasonable extension along lymphatic drainage (~5 cm proximally and ~2–5 cm distally), depending upon regions involved. The optimal RT dose has also not been defined. The *National Comprehensive Cancer Network* (NCCN) recommends a dose of 30–36 Gy [10] and the European Society for Medical Oncology (ESMO) a dose of 30 Gy [11].

Resection followed by observation has been evaluated in children. The EuroNet-PHL reported data on 58 children treated with surgery alone. The progression free survival (PFS) was 57% at 50 months. All patients with incomplete resection relapsed (median 17 months) but the OS was

Table 1. Selected studies in stages I–II NLPHL

	N	Median follow-up (years)	Treatment	Outcome (%)			OS (%)	Comments
Chen RC, Chin MS, Ng AK, *et al*. Early stage, lymphocyte-predominant Hodgkin's lymphoma: patient outcomes from a large, single institution series with long follow-up. *J Clin Oncol.* 2010; **28:**136–141.	113	11.3	RT 82% CMT 12% CHT 6%	10 yr	PFS	Limited RT, 64 Regional RT, 84 Extended RT, 81 CHT only, 14	Limited RT, 100 Regional RT, 95 Extended RT, 95 CHT only, 83	Extent of RT did not impact PFS or OS. CMT did not affect PFS but was associated with worse OS
Nogova L, Reineke T, Eich HT, *et al*. Extended field radiotherapy, combined modality treatment or involved field radiotherapy for patients with stage IA lymphocyte-predominant Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Study Group (GHSG). *Ann Oncol.* 2005;**16:**1683–1687.	131	3.6	RT 69% CMT 31%	2 yr	FFTF	EFRT, 100 IFRT, 92 CMT, 97	100	Included only stage IA without risk factors
Feugier P, Labouyrie E, Djeridane M, *et al*. Comparison of initial characteristics and long-term outcome of patients with lymphocyte-predominant Hodgkin lymphoma and classical Hodgkin lymphoma at clinical stages IA and IIA prospectively treated by brief anthracycline-based chemotherapies plus extended high-dose irradiation. *Blood.* 2004;**104:**2675–2681.	42	NA	CMT	15 yr	FFP	80	86	Brief chemo and EFRT
Wilder RB, Schlembach PJ, Jones D, *et al*. European Organization for Research and Treatment of Cancer and Groupe d'Etude des Lymphomes de l'Adulte very favorable and favorable, lymphocyte-predominant Hodgkin disease. *Cancer.* 2002; **94:**1731–1738.	48	9.3	RT 77% CMT 23%	10 yr	RFS	RT, 77 CMT, 68	90 100	Variable radiation field size
Wirth A, Yuen K, Barton M, *et al*. Long-term outcome after radiotherapy alone for lymphocyte predominant Hodgkin lymphoma: a retrospective multicenter study of the Australasian Radiation Oncology Lymphoma Group. *Cancer.* 2005; **104:** 1221–1229.	202	15	RT	15 yr	FFP	82	83	No effect of radiation field size
Savage KJ, Skinnider B, Al-Mansour M, *et al*. Treating limited stage nodular lymphocyte predominant Hodgkin lymphoma similarly to classical Hodgkin lymphoma with ABVD may improve outcome. *Blood.* 2011; **118:** 4585–4590.	51 35	5.7 18.6	CHT ± RT RT only	10 yr	PFS	93 77.5	93 85	Patients treated with CHT only had negative interim PET scans
Shankar A, Hall GW, Gorde-Grosjean S, *et al*. Treatment outcome after low intensity chemotherapy [CVP] in children and adolescents with early stage nodular lymphocyte predominant Hodgkin's lymphoma - an Anglo-French collaborative report. Eur J Cancer. 2012; **48:** 1700–1706.	55	3.3	CHT	3.3 yr	FFTF	75.4	100	All children, <18 yr

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Table 1. (Continued)

	N	Median follow-up (years)	Treatment	Outcome (%)			OS (%)	Comments
Mauz-Korholz C, Gorde-Grosjean S, Hasenclever D, *et al*. Resection alone in 58 children with limited stage, lymphocyte-predominant Hodgkin lymphoma-experience from the European network group on pediatric Hodgkin lymphoma. Cancer. 2007; **110:** 179–185.	58	3.6	Excision	4.2 yr	PFS	57	100	All children, <18 yr
Appel B, Ehrlich P, Chen L, *et al*. Treatment of pediatric stage IA lymphocyte-predominant Hodgkin lymphoma with surgical resection alone: A report from the Children's Oncology Group. *ASCO Meeting Abstracts*. May 30, 2012 2012;30(15_suppl):9524	52	NA	Excision	2 yr	EFS	88	100	Patients with completely resected stage 1A disease
Advani RH, Horning SJ, Hoppe RT, *et al*. Mature results of a phase II study of rituximab therapy for nodular lymphocyte predominant Hodgkin lymphoma. *J Clin Oncol*. 2014; **32:** 912–918.	14	7.3	Rituximab	–	Median PFS	5.6 yr	NA	Included stage 1 and 2 patients ~ 50% of patients received rituximab maintenance
Eichenauer DA, Fuchs M, Pluetschow A, *et al*. Phase 2 study of rituximab in newly diagnosed stage IA nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin Study Group. Blood. 2011; **118:** 4363–4365.	28	3.6	Rituximab	1 &3 yr	PFS	96.4 & 81.4	100	All patients with stage 1A disease

Legend: NHPHL, nodular lymphocyte predominant Hodgkin lymphoma; FFTF, freedom from treatment failure; FFP, freedom from progression; PFS, progression free survival; RFS, recurrence free survival; EFS, event free survival; OS, overall survival; IFRT, involved field radiotherapy; EFRT, extended field radiotherapy; RT, radiotherapy; CMT, combined modality therapy; CHT, chemotherapy; NA, not reported/not available; yr, years.
Adapted from Advani RH, Hoppe RT. How I treat nodular lymphocyte predominant Hodgkin lymphoma. Blood. 2013; 122: 4182–4188.

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Table 2. Selected studies in stages III–IV NLPHL

	N	Median follow-up (Years)	Treatment	Outcome (%)			OS (%)
Diehl V, Sextro M, Franklin J, *et al*. Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease and lymphocyte-rich classical Hodgkin's disease: report from the European Task Force on Lymphoma Project on Lymphocyte-Predominant Hodgkin's Disease. *J Clin Oncol.* 1999;17(3): 776–783.	44	6.8	CHT or CMT*	8 yr	FFTP	Stage III, 62 Stage IV, 24	Stage III, 94 (DSS) Stage IV, 41 (DSS)
Nogova L, Reineke T, Brillant C, *et al*; German Hodgkin Study Group. Lymphocyte-predominant and classical Hodgkin's lymphoma: a comprehensive analysis from the German Hodgkin Study Group. *J Clin Oncol.* 2008;26(3): 434–439.	83	4.2	CMT	4.2 yr	FFTF	77	96
Canellos GP, Mauch P. What is the appropriate systemic chemotherapy for lymphocytepredominant Hodgkin's lymphoma? *J Clin Oncol.* 2010; 28:e8.	37	NA	32%, ABVD or EVA 68%, MOPP ± ABVD	–	'Failure' 'Failure'	75 32	NA NA
Fanale MA, Lai C-M, McLaughlin P, *et al*. Outcomes of Nodular Lymphocyte Predominant Hodgkin's Lymphoma (NLPHL) Patients Treated with R-CHOP. ASH Annual Meeting Abstracts. 2010;116: 2812.	12	3.5	RCHOP ± IFRT	5 yr	PFS	95	95
Xing KH, Connors JM, Al-Mansour M, *et al*. The outcome of advanced stage nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL) compared with classical Hodgkin's lymphoma (cHL): a matched pair analysis. *Blood.* 2014; 123: 3567–3573	42	10	83%, ABVD	10 yr	FFTF	76	86

Legend: 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, isophosphamide, 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.

Adapted from Advani RH, Hoppe RT. How I treat nodular lymphocyte predominant Hodgkin lymphoma. Blood. 2013; 122: 4182–4188.

100%. The Children's Oncology Group study reported 52 patients with completely resected stage IA disease. The 2-year event free survival and OS were 88 and 100% respectively. These data suggest that observation may be an option in carefully selected patients with stage I disease, but this is not considered standard practice, because most of these patients will relapse.

There are no prospective studies comparing combined-modality therapy (CMT) with RT alone in early stage NLPHL. Retrospective studies from the MD Anderson, the GHSG, and Harvard failed to show improvement in outcome with CMT compared with RT alone (Table 1). In contrast, a retrospective study from the BC Cancer Agency (BCCA) comparing RT alone with chemotherapy (usually ABVD) (adriamycin, bleomycin, vinblastine, dacarbazine) with or without RT showed an improvement at 10 years in both PFS and OS using a chemotherapy-based approach

Limited paediatric data have utilized chemotherapy alone with 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 BCCA, no relapses were identified among 14 patients treated with ABVD alone in the presence of an interim negative positron emission tomography scan. While these results are provocative, the follow-up was short for this disease, which is often associated with late relapse.

The universal expression of CD 20 has led to evaluation of rituximab as a single agent. In a prospective trial of the GHSG, 28 patients with stage IA disease received four weekly standard doses of rituximab with an overall

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response rate (ORR) of 100%; however, 25% of patients relapsed (median follow-up 43 months). A prospective trial from Stanford included 13 previously untreated patients [6,8]. The response rate was 100%, and the relapse rate was similar to that reported by the GHSG. These results indicate that rituximab is effective, but as a single agent, responses are not durable and are inferior to those achieved by RT or CMT and therefore not recommended as primary therapy for patients with newly diagnosed, early stage disease.

Treatment of advanced stages (Table 2)

Advanced stage NLPHL occurs in 20–25% patients. It is important to evaluate clinical history and sites of disease, because of possibility of occult transformation [5,7]. The NCCN Guidelines [10] include a broad range of options for advanced disease that depend upon the goals of therapy. The ESMO Guidelines consider management to be the same as for classical Hodgkin lymphoma (cHL) [8,11].

Chemotherapy with regimens similar to those used for cHL is the mainstay of treatment (Table 2). Most data are retrospective and include studies conducted across several decades. The largest series from the GHSG compared outcomes of 83 patients with NLPHL to 3083 with cHL from their prospective trials. Chemotherapy varied and included COPP, COPP/ABVD, COPP/ABV/IMEP (ifosphamide/methotrexate/etoposide/prednisone), and BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) (baseline and escalated), all of which contain significantly higher doses of alkylating agents than ABVD. There were no significant differences in FFTF rates for patients with NLPHL or cHL (77 and 75% respectively, $p = 0.46$). The BCCA reported an analysis of 42 patients treated with ABVD or ABVD-like chemotherapy The 10-year OS ($p = 0.57$) and the Hodgkin lymphoma–FFTF were similar between NLPHL and cHL (75 vs 73%, $p = 0.6$). However, the time to progression, which also included development of aggressive lymphomas, was inferior in NHLPL 63 versus 73%, $p = 0.04$) and was worse for patients with splenic involvement (48 vs 71%).

The choice of chemotherapy for NLPHL is controversial with some studies suggesting that alkylator-based therapy is superior to ABVD. In a retrospective analysis from the Cancer and Leukemia Group B, 37 patients were treated with MOPP [mechlorethamine, vincristine, procarbazine, prednisone), MOPP/ABVD or ABVD/EVA (etoposide, vinblastine, adriamycin)] [12]. 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. At the MD Anderson Cancer Center, 15 patients were treated with RCHOP (rituximab, cyclophosphamide, adriamycin, vincristine, prednisone) with no episodes of relapse or transformation observed at a median follow up of 42 months.

Rituximab as single agent has also been evaluated in front line therapy in advanced stage disease. Although the ORR was 100%, the median PFS was only 22 months (range: 8–74 months), suggesting that responses with rituximab are not as durable as those achieved with chemotherapy or CMT and is not recommended as monotherapy in front line setting unless used in a palliative setting [7]. RT may also serve a palliative benefit in advanced disease.

Treatment of relapsed NLPHL

Late relapses occur more commonly in patients with NLPHL than cHL, but standard treatment for these patients is not well defined [1,6,8,13]. Biopsy documentation of clinical relapse is essential to exclude progressive transformation of germinal centres or transformation to an aggressive B-cell lymphoma. Therapy decisions depend on multiple factors, including prior therapy, response duration, treatment intent, and comorbidities. A subset of patients may develop chronic relapsing disease, often with limited extent in peripheral nodes. Palliative management is appropriate for this group. Other treatment modalities, such as localized RT, conventional chemotherapy, or CMT may also be options, although there are no large series published to date.

Data on high-dose chemotherapy followed by *autologous stem cell transplant* for relapsed NLPHL are limited. A study on 26 patients with relapsed NLPHL (33% with transformation to a large cell lymphoma) treated with high-dose chemotherapy and autologous stem cell transplant reported at a median follow-up of 50 months, a 5-year OS, and event free survival of 76 and 69% respectively [14].

Prospective studies have evaluated the role of rituximab in the relapsed setting. At Stanford, a phase II study included 18 patients with relapsed NLPHL treated with four weekly doses of rituximab at standard doses ($n = 11$) or rituximab plus maintenance therapy for 2 years ($n = 7$). The ORR to induction therapy was 100% (complete response, 78%) [7]. The estimated 5-year PFS of the patients treated with maintenance rituximab was not statistically significantly superior to the use of rituximab induction therapy alone. The median OS was not reached for either group. In a study conducted by the GHSG, 15 patients with relapsed NLPHL received four weekly standard doses of rituximab. All but one patient responded to treatment. The median time to progression was 33 months, and the median OS was not reached [15]. Together, these data suggest that treatment with rituximab alone can achieve an excellent initial response, but this therapy is not curative and a continuous pattern of relapse is seen, even with

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maintenance rituximab. However, given the excellent tolerance to this agent, rituximab monotherapy in the relapse setting is a reasonable consideration.

Conclusions

NLPHL is rare, with few prospective trials to guide therapy. The majority of patients present with early stage disease and treatment with local radiation provides excellent disease control and OS. For locally extensive or advanced stages, paradigms used for cHL have been employed with similar outcomes, with some suggestion that alkylator-intensive regimens may be preferable to ABVD. Expression of CD20 in NLPHL has led to the evaluation of rituximab as a therapeutic option. While 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 ORR and excellent tolerability. Unlike cHL, late relapses may occur, as well as a propensity to transform to an aggressive B cell NHL that underscores the importance of long-term follow-up, as well as re-biopsy at the time of relapse. Deaths because of NLPHL are uncommon; therefore, overall goals of therapy should be to minimize the risk of relapse and reduce long-term toxicity. Treating physicians need to recognize the unique features of this disease in order to deliver optimal therapy.

Conflict of interest

Ranjana Advani receives research funding from Genentech.

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