The emerging role for rituximab in the treatment of nodular lymphocyte predominant Hodgkin lymphoma
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Introduction
The development and utilization of immunohistochemistry led to the first distinction between classical Hodgkin’s disease, including a lymphocyte-rich variant, and lymphocyte predominant Hodgkin’s disease in the 1994 Revised European-American Lymphoma (REAL) classification [1]. According to the current World Health Organization (WHO) criteria, Hodgkin lymphoma is subdivided into nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL). These entities substantially differ in their morphology, immunophenotypic characteristics, and clinical behavior.

Clinically, NLPHL is rare and represents approximately 5% of all Hodgkin lymphomas. Approximately, 400 patients are diagnosed each year in the United States. NLPHL has a marked male predominance and presents with limited stage and peripheral lymphadenopathy. Unlike cHL, systemic symptoms and mediastinal or bone marrow involvement are uncommon and there is a propensity for late relapses.

Pathologically, NLPHL is characterized by a nodular or nodular and diffuse proliferation of scattered large neoplastic cells called ‘popcorn’ or lymphocyte predominant cells (formerly called lymphocytic and histiocytic cells), which consistently express the B-cell antigen CD20. The nodules represent progressively transformed germinal centers, and according to the current WHO definition, at least a partial nodular pattern is required for a diagnosis of NLPHL [2]. Immunostaining for CD20 can detect lymphocyte predominant cells and identify nodules in specimens that may appear to have a completely diffuse morphology.

Unlike the malignant Reed–Sternberg cells seen in cHL, lymphocyte predominant cells lack expression of CD15 and CD30. The J chain is present in the majority of cases and epithelial membrane antigen (EMA) is present in over one-half of the cases [3].

Although Reed–Sternberg cells and lymphocyte predominant cells are markedly different by immunohistochemical analysis, they are closely related according to their gene expression profiles (GEP) and likely share similar pathogenic mechanisms. Both Reed–Sternberg and lymphocyte predominant cells are characterized by downregulation of B-cell lineage-specific genes, and lymphocyte predominant cells are similar to T-cell-rich large B-cell lymphoma (TCRBCL) on GEP [4]. NLPHL can be difficult to differentiate from TCRBCL, and
reactive hyperplasia or progressive transformation of germinal centers can precede or follow a diagnosis of NLPHL [2]. Transformation to large B-cell lymphoma has been reported in 5–10% of cases, and in 50% of cases specifically to the TCRBCL type [5]. A prominence of extranodal lymphocyte predominant cells in NLPHL is reported to be associated with an increased likelihood for development of TCRBCL and overlap between NLPHL and TCRBCL may occur concurrently in the same specimen [2,5]. These attributes underscore the need for review by expert hematopathologists and the importance of repeating a biopsy for recurrent disease.

**Therapy**

Traditionally, NLPHL has been included with cHL in prospective trials and excellent prognosis has been reported in several series. In a retrospective review by the European Task Force on Lymphoma (ETFL), 219 stage I/II NLPHL patients were treated with radiotherapy and/or chemotherapy using standard Hodgkin lymphoma protocols with an excellent 10-year overall survival (OS) of more than 90%. Despite high survival rates, late relapses were observed more frequently than in cHL [6]. Another observation was the development of late treatment-related effects, especially secondary malignancies and cardiac toxicities. Only 4% of NLPHL patients died of disease, whereas an equal number died of fatal secondary leukemia or solid tumors [7]. In an analysis of eight series of patients treated for NLPHL, death from NLPHL (6%) was as common as death from second malignancies (6%) or from other causes (6%) [8].

For early stage patients, several groups have studied less toxic treatments such as the watch and wait approach and involved field radiotherapy. A French phase II study of children with stage IA NLPHL demonstrated that though event-free survival was significantly better for combined modality therapy compared with a watch and wait approach after surgical lymphadenectomy (90 versus 42%, respectively, \(P < 0.04\)), there was no difference in OS between the two groups [9].

In a recent retrospective analysis of 394 patients with NLPHL (63% favorable early stage, 16% unfavorable early stage, 21% advanced stage) compared with 7904 patients with cHL treated on the German Hodgkin Study Group (GHSG) trials HD4–HD12, NLPHL patients had a better freedom from treatment failure (FFTF: 88 versus 82%, \(P = 0.0092\)) and OS (96 versus 92%, \(P = 0.016\)) [10]. Consistent with the ETFL report, this study also reported a significantly higher incidence of late relapses (7.4 versus 4.7%, \(P = 0.0226\)).

Currently, the optimal treatment for NLPHL remains uncertain. According to the National Comprehensive Cancer Network (NCCN) guidelines, involved field radiotherapy alone is recommended for early stage disease, and for advanced stages, chemotherapy alone or combined with radiotherapy similar to that used in cHL [11]. The expression of CD20 in NLPHL lends itself to the evaluation of the role for anti-CD20 approaches and emerging data suggest that that rituximab, a chimeric monoclonal antibody, used in non-Hodgkin lymphoma may have a role in the treatment of NLPHL.

**Rituximab**

The use of the chimeric monoclonal anti-CD20 antibody rituximab has been studied in several recent trials, which are summarized in Table 1 [12,13,14,15,16]. The first report

<table>
<thead>
<tr>
<th>Citation</th>
<th>Rituximab schedule* (N)</th>
<th>Disease status</th>
<th>Prior therapy</th>
<th>% ORR/CR or CRu</th>
<th>PFS/median follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rehwald et al. [12]</td>
<td>Standard (14)</td>
<td>Relapsed</td>
<td>COPP, ABVD, CHOP, VIP-E, MOPP, BEACOPP, OPPA, splenectomy, transplant</td>
<td>86/57</td>
<td>NR/12</td>
</tr>
<tr>
<td>Schultz et al. [13]</td>
<td>Standard (15)</td>
<td>Relapsed</td>
<td>Radiotherapy, chemotherapy, splenectomy (exact regimens not specified)</td>
<td>94/54</td>
<td>33/63</td>
</tr>
<tr>
<td>Ekstrand et al. [14]</td>
<td>Standard (22)</td>
<td>Untreated (n = 12); relapsed (n = 10)</td>
<td>MOPP, ABVD, MOPP/ABVD, CHOP, radiotherapy</td>
<td>100/45</td>
<td>10.2/13</td>
</tr>
<tr>
<td>Horning et al. [15]</td>
<td>Standard (23)</td>
<td>Untreated (n = 21); relapsed (n = 18)</td>
<td>Not specified</td>
<td>97/56</td>
<td>24/72</td>
</tr>
<tr>
<td>Azim et al. [16]</td>
<td>Extended (16)</td>
<td>Untreated (n = 2); relapsed (n = 5)</td>
<td>VBM, ABVD, ChlVPP, ABVVP16, splenectomy, radiotherapy</td>
<td>97/88</td>
<td>NR/30</td>
</tr>
</tbody>
</table>

* Radiotherapy: involved field (IF): regional; or subtotal lymphoid (STL); ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ABVVP16, adriamycin, bleomycin, vinblastine, etoposide; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ChlVPP, chlorambucil, procarbazine, prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone, vincristine; COPP, cyclophosphamide, vincristine, procarbazine, prednisone; CR, complete remission; CRu, complete remission unconfirmed; ESHP, etoposide, methylprednisolone, Ara-C, cisplatin; MOPP, mechloethamine, vincristine, procarbazine, prednisone; NR, not reached; OPPA, doxorubicin, procarbazine, prednisone, vincristine; PFS, progression-free survival; VBM, vinblastine, methotrexate, bleomycin; VIP-E, etoposide, ifosfamide, cisplatin, epirubicin.

* Rituximab schedule: standard rituximab = rituximab 375 mg m\(^{-2}\) weekly × 4. Extended rituximab = 375 mg m\(^{-2}\) weekly × 4, repeated at 6-month intervals for 2 years.
* Three patients received combination chemotherapy (ESHAP, ABVD, or chlorambucil) and rituximab. Five patients received monthly maintenance rituximab for at least 4 months.
* Includes 22 patients from prior report [14].
of a patient with relapsed NLPHL treated with rituximab was published in 1999 [17]. This patient with stage IV disease at the time of treatment achieved a complete response for 6 months with standard dosing of rituximab. Subsequently, two series have reported their experiences; one from the GHSG and the other from Stanford University.

The GHSG conducted a phase II study between 1999 and 2004 investigating the activity of rituximab (375 mg/m² weekly for 4 weeks) in 21 relapsed or refractory NLPHL patients. In 2002, an interim analysis of 14 patients at a median follow-up of 12 months reported an overall response rate (ORR) of 86%. At the time of the publication, the median duration of response had not been reached at 20+ months [12]. The therapy was well tolerated with mild grade 1–2 infusion-related adverse effects such as chills and fever in 79% of the patients. In a follow-up report in 2007, a pathology review confirmed NLPHL in only 15 of 21 patients enrolled, whereas six patients were reclassified as Hodgkin lymphoma transformed to TCRBCL or CD20+ cHL and were excluded from the final analysis. Nine of these 15 patients had stage I/II disease and six stage III/IV disease, with a median time after first diagnosis of 12 years. Patients were in first or higher relapse or had progressive disease after at least one standard regimen, including radiation (n = 7); radiation and chemotherapy (n = 3); chemotherapy (n = 3); chemotherapy and splenectomy (n = 1); or chemotherapy, splenectomy, and radiation (n = 1). Remission status was checked 4 weeks after the end of rituximab treatment, every 3 months for 2 years, every 6 months until the fifth year, and then annually. At a median follow-up of 63 months (range 3–84 months), the ORR was 94% (100% for stage I/II and 83% for stage III/IV patients), with a median time to progression (TTP) of 33 months [13**]. At the time of publication, the median OS had not been reached [13**].

Similar results have been reported in a prospective phase II study conducted at Stanford University from 1999 to 2002, in 22 patients with untreated or relapsed NLPHL [14]. Of the 12 treatment-naive patients, four had stage 1 disease, three stage II, and five stage III. Of the 10 patients with relapsed disease (three stage I, four stage II, and three stage III disease), prior therapy included either radiotherapy alone (involved field, regional, or subtotal lymphoid irradiation), chemotherapy, or combined modality therapy (Table 1). A standard dose of 4 weekly infusions of rituximab at 375 mg/m² was used. At a median follow-up of 13 months (range 3–32 months), the ORR was 100% [45% complete response (CR), 54% partial response] with no difference in response between treatment-naive patients or those who had relapsed after standard chemotherapy and/or radiotherapy. In contrast to the reports of the GHSG, the duration of response was relatively brief, with a TTP of 10.2 months, likely related to differences in patient populations. In contrast to the GHSG study, the Stanford study included both treatment-naive and relapsed patients, and 41% of the former group had advanced disease and/or three or more nodal sites of disease, which is unusual as most patients present with limited stage disease. Overall, rituximab was well tolerated with hematologic toxicity limited to grade 1, and no grade 3 or 4 toxicities. Although the small sample size makes subset analysis difficult to interpret, age, sex, extent of disease, and previous treatment did not appear to correlate with likelihood of relapse. Nine patients relapsed and five of these were rebiopsied. Three patients had recurrent NLPHL, whereas two demonstrated evidence of transformation to large cell non-Hodgkin lymphomas: TCRBCL (n = 1) and diffuse large B-cell lymphoma (n = 1).

In an attempt to improve the response duration, this protocol was subsequently modified to include extended rituximab treatment after standard dosing consisting of 4 weekly 375 mg/m² doses at 6-month intervals for 2 years, similar to the strategy employed in low-grade lymphomas [18]. Restaging studies after the completion of all treatment were performed at 1, 3, and 6 months, and every 6 months thereafter to progression. A recent analysis of 39 patients [standard rituximab dosing (n = 23) and extended rituximab (n = 16)] reported at a median follow-up of 60 months a 97% ORR (69% complete response (CR)) with a 10-year and 20-year OS of 97 and 85%, respectively [15]. Complete response (CR) was achieved in 88% of patients treated with extended rituximab compared with 56% with standard rituximab dosing (P = 0.08), with no difference in responses comparing previously treated versus untreated patients. Seventeen patients progressed (15 treated with standard dosing and two with extended rituximab). The median TTP was 24 months for standard treatment and had not been reached for patients treated with extended rituximab (P = 0.03). The use of extended rituximab significantly improved the TTP in this series.

Earlier this year, a third experience by Azim et al. [16*] reported a retrospective analysis in a subset of NLPHL patients treated at the European Institute of Oncology with rituximab as a single agent or with combination chemotherapy. Of 26 patients with NLPHL treated between 1999 and 2007, seven received rituximab [four as a single agent and three in combination with chemotherapy, including chlorambucil monotherapy, combination etoposide, methylprednisolone, Ara-C, and cisplatin (ESHAP), and doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD)]. Two patients were treatment-naive, whereas five had relapsed disease. All patients received induction rituximab at the standard dose of 375 mg/m² weekly for 4 weeks, and five patients went on to receive monthly maintenance for at least 4 months. The ORR was 100%, and six of seven patients achieved a complete response. At a median follow-up of
2 years (range 1–48 months), the median TTP was 27 months (range 4–35 months).

Collectively, these data suggest that rituximab is an active agent in NLP HL both in the upfront and relapsed setting.

Conclusion

NLP HL is a unique entity with excellent long-term outcomes despite a propensity for late relapses. Although a management approach akin to cHL is successful, it is important to develop therapies in which the late effects of treatment can be minimized. Long-term monitoring of these patients for both disease recurrence and second malignancies is critical.

Rituximab is an effective alternative therapy for NLP HL that may be associated with fewer long-term adverse events. The emerging efficacy data in both the treatment-naive and relapsed patient populations are promising and this agent appears to be highly active and well tolerated. These results pave the way for better defining the role of anti-CD20-targeted therapies as single agents or in combination with chemotherapy and/or radiotherapy. Its efficacy may allow for use as a single agent for upfront treatment of early stage disease after surgical excision or potentially with a lower dose of involved field radiotherapy than traditionally used. For advanced disease, the combination of rituximab with chemotherapy may allow for reducing the number of chemotherapy cycles, thereby reducing toxicity. Newer generations of anti-CD20-targeted therapies with engineered antibodies or radio-labeled molecules require testing, and such studies are ongoing. Preliminary data suggest that 131I-tositumomab may also have activity in cHL and NLP HL [19]. Due to the rarity of NLP HL and its indolent natural history, long-term follow-up of these data will be needed to truly assess the benefits and risks of rituximab use and better define its role and that of other anti-CD20-targeted therapies in the optimal treatment of NLP HL.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 475–477).


14 This is an update of the GHSG phase II study of standard dose rituximab in relapsed NLP HL. This series reports the longest progression-free survival (PFS) reached to date for the use of rituximab in this study population.


18 This is the most recent publication investigating the role of rituximab in treatment-naive or relapsed NLP HL patients.

