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REVIEW ARTICLE

Management of nodular lymphocyte-predominant Hodgkin lymphoma: recommendations and unresolved dilemmas

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Abstract

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare malignancy of young adults characterized by an indolent and recurrent course. Although relapses or transformation to aggressive B cell lymphoma can occur decades after the primary diagnosis, the prognosis of NLPHL is relatively good, with as much as a 90% 10-year overall survival rate. The rarity of NLPHL makes it difficult to conduct multicenter prospective studies to establish separate guidelines for the diagnosis and treatment of this disease.

Therefore, the recommendations for the treatment of NLPHL have for many years been the same as for classic Hodgkin lymphoma, except for early stages without risk factors. The registration of anti-CD20 monoclonal antibody for the treatment of CD20-positive B-cell lymphomas has opened up new perspectives for NLPHL patients. Modern and accurate histopathological examinations as well as imaging diagnostics, especially positron emission tomography/computed tomography has allowed a more precise distinction to be made between the indolent NLPHL and the transforming-to-aggressive lymphoma forms. This review is intended to provide readers with the clinical features, course, outcome and methods of standard treatment in patients with NLPHL. The author in particular wishes to draw attention to unresolved issues regarding standard management and also the use of active surveillance, anti-CD20 immunotherapy, less aggressive regimens of chemotherapy, and indications for new treatment options.

Key words: NLPHL, radiotherapy, immunochemotherapy, new agents

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Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) accounts for 5% of Hodgkin lymphoma (HL). In contrast to classic Hodgkin lymphoma (cHL), it is characterized by an indolent and recurrent course. Although late relapses and transformation to diffuse large B cell lymphoma (DLBCL) can occur, NLPHL prognosis is relatively good. Based on long term data from multicenter registries, 10-year overall survival is 57–99% depending on the clinical stage of the disease and the time of treatment initiation (i.e. whether within 12 months of diagnosis) [1]. Unlike cHL, NLPHL relapses can occur many years after initial or subsequent lines of therapy. NLPHL is a rare neoplasm, with a crude incidence in Europe of 2.3 per 100,000 per year [2]. In 2018, 659 cases of HL were registered to the Polish National Cancer Registry. This corresponds to up to 30 new cases per year of NLPHL in Poland [3]. Adequate surgical biopsy of lymph node for formalin-fixed sample is required for a diagnosis of NLPHL. In the histological examination malignant cells termed lymphocyte-predominant cells (LP cells, popcorn cells)

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are located in the background of small B lymphocytes, rosetting PD1+ T-cells, epithelioid histiocytes, and follicular dendritic cells. LP cells are germinal centers of origin with B cell markers expression (positive for CD20, CD45, CD79a, PAX5, OCT2, BOB1, BCL6; negative for CD15 and CD30).

According to the 2016 revision of the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues, the variant of growth pattern should be noted in the diagnostic report: 75% of NLPHL cases show typical nodular growth pattern (classical B-cell rich nodular: A or serpiginous: B), but 25% present different histology patterns (C, D, E, or F) with diffuse infiltrates or nodules dominated by surrounding T-cells. Cases of typical histological growth patterns demonstrate localized disease and a better prognosis in terms of increased response rate and progression-free survival (PFS) compared to variant histology patterns. NLPHL of variant histology has to be carefully distinguished from aggressive B-cell T cell-rich lymphoma [4, 5].

NLPHL is typically recognized in children and young males aged 30–40. Approximately 75% of cases are limited according to Ann Arbor stage I/II with lymph nodes involvement. Mediastinal, extranodal, bulky disease or B symptoms are uncommon [1, 6, 7].

Transformation to aggressive B cell lymphoma is a constant feature of NLPHL. It may be present at initial diagnosis simultaneously with the NLPHL pattern. Therefore, representative surgical biopsy is essential for a reliable diagnosis.

The risk of transformation to aggressive B cell lymphoma has been reported to be 31% over 20 years of NLPHL follow up [8]. Because the transformation can occur at any relapse and in follow up, even decades after the initial NLPHL diagnosis, re-biopsy is necessary whenever a relapse is suspected.

NLPHL still poses a challenge for hemato-oncologists. Treatment recommendations by the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) are partly in line with cHL guidelines. But indolent presentation of NLPHL could favor non-aggressive approaches such as surgical resection with a watch-and-wait strategy (IA), local radiotherapy, or rituximab monotherapy [2, 9]. On the other hand, the tendency for recurrence and the occurrence of transformations may require more aggressive treatment: immunochemotherapy with rituximab (R) combined with radiotherapy (RT) [10]. The rare occurrence of NLPHL, and the unavoidably long follow-up, somewhat preclude organizing prospective trials which could result in establishing evidence-based recommendations for first or salvage lines of treatments. This review discusses the current treatment options for patients with NLPHL.

Staging and risk factors

Clinical staging of NLPHL is based on the Lugano classification based on Ann Arbor staging with Cotswolds modification [11]. The risk groups are often extrapolated from cHL according to EORTC/LYSA and German Hodgkin Study Group (GHSG) scales [2]. Additionally, the German Study Group has proposed a prognostic scale including three adverse risk factors: male gender (2 points); low serum albumin level (1 point); and variant growth pattern C–F (1 point). Patients are divided into three risk groups: low (0–1 point); intermediate (2 points); and high (3–4 points) with estimated 5-year PFSs of 95%, 88% and 69% respectively. The histopathology growth pattern is an independent prognostic factor of progression or relapse, but it has not influenced the choice of NLPHL treatment thus far. The same applies to other points of the scale [5]. Also, age above 45 years at presentation, advanced stage, low hemoglobin level, and systemic symptoms are considered adverse factors in terms of overall survival (OS) [6, 8]. The risk of transformation to aggressive B cell lymphoma is approximately 7% in 10 years of observation, and 31% in 20 years of NLPHL follow up. The risk is higher in bulky disease and splenic involvement [8].

In everyday clinical practice, the type of therapy for newly diagnosed NLPHL is stratified according to disease stage and risk factors. Three groups are distinguished: non-bulky (<10 cm) early stage NLPHL; early stage; and advanced disease. In non-bulky early stage, NLPHL is in clinical stage (CS) I or II with contiguous disease without related symptoms and threat of organs compromise. CSs III and IV according to the Ann Arbor scale are defined as advanced NLPHL. Early stage with risk factors (intermediate risk group) are situations in between.

Recommendations: first line treatment

Early stages without risk factors: CS IA/ /contiguous IIA

Approximately half of patients with NLPHL are early stage without risk factors. According to the ESMO recommendation for patients with CS IA, standard treatment is ISRT (involved site radiotherapy) 30 Gy alone. Based on retrospective data of the GHSG, 8-year PFS and OS for patients with stage IA is 91.9% and 99% for involved field radiotherapy (IF-RT) [12]. Patients with CS IIA contiguous disease treated with radiotherapy alone also have good prognosis.

Moreover, observation after complete excision of lymph node can be considerable for selected groups of patients in early stages without risk factors. Retrospective studies show a 10-year OS rate of 91% in these circumstances [13].

Early stages with risk factors and advanced stages

There are several options for induction treatment of NLPHL patients in the early stages with risk factors and in advanced stages. ABVD chemotherapy can be considered. The GHSG recommends interim-PET/CT guided eBEACOPP for advanced stage [14]. Others suggest the use of

chemotherapy with anti-CD20 antibody RCHOP [10] or in some selected cases RCVP [15] or R bendamustine [16]; these issues are discussed later. Immunochemotherapy lasting 3–4 months with or without radiotherapy can be considered in early stages; longer treatment should be applied in advanced stages. According to the NCCN guidelines, observation is advised for advanced NLPHL asymptomatic patients after making individual decisions.

Transformed NLPHL

In a case of upfront transformation, RCHOP is recommended with efficiency comparable to induction strategy for DLBCL [13].

Evaluation of response after first-line treatment

According to the Cheson criteria, PET/CT should be incorporated in the staging and assessment of efficacy of induction therapy. If radiotherapy was planned, contrast-enhanced CT is mandatory in the staging period. The re-biopsy of suspected NLPHL sites should be obtained in cases of stable or progressed disease after initial treatment. Also, the verification of recurrence by histopathological examination is essential to exclude transformation to aggressive cHL in further course of the disease.

Recommendations: relapsed NLPHL

The initiation of salvage therapy must be preceded by the histopathological verification of NLPHL recurrence. To precisely describe the clinical stage of the relapsed disease, contrast-enhanced CT of the neck, chest and abdomen with pelvis, or PET/CT, is recommended.

In localized relapses, radiotherapy can be used. Also, monotherapy with rituximab can be considered [17]. Salvage systemic therapy has to be chosen individually, according to several factors: patient performance status, extent of disease relapse, disease symptoms, and type of previous treatment [18]. The optimal chemotherapy regimen used for the second line in NLPHL is not defined. The implementation of anti-CD20 monoclonal antibody is essential for cases with no previous anti-CD20 exposure and if relapse is more than six months after prior anti-CD20 therapy. The role of autologous transplant (AHCT) in not clearly defined in recommendations, but it remains a PET/CT guided therapeutic option, the same as in cHL [9]. Patients with transformation to DLBCL should be managed according to recommendations for relapsed/refractory DLBCL. In that case, the role of AHCT is clear.

Unresolved dilemmas in treatment of NLPHL

Early stages

Various treatment options have been evaluated in the early stages. According to ESMO and NCCN, radiotherapy alone is the standard treatment for early favorable NLPHL. Several reports show that the addition of chemotherapy or other variants of induction strategy in early favorable stages do not improve patient outcomes [12, 19–22]. For instance: in a multicenter retrospective database of stage I/II NLPHL diagnoses over a 20-year period, the outcome of 559 patients was analyzed. Patients underwent radiotherapy, chemotherapy, combined modality treatment (radiotherapy with chemotherapy), observation after surgical excision, rituximab and radiotherapy or as a single agent. 5-year PFS was 87.1% in the entire group, and 5-year OS was 98.3%. 5-year PFS for different kinds of induction strategies were: 91.1% in the radiotherapy group; 90.5% after chemotherapy with radiotherapy; 77.8% after chemotherapy; 73.5% in the observation group; 80.8% after rituximab with radiotherapy; and 38.5% after rituximab alone [23].

For selected groups of patients, total surgical resection followed by a careful watch-and-wait strategy (active surveillance) is reasonable. This kind of management is purposely chosen in pediatric and young adult groups to avoid potential acute and long-term toxicity e.g. maturation disorders or secondary malignances. In 163 consecutive patients, 37 (23%) were observed. 23 of them were in early stage, and 14 advanced. 5-year PFS was 77% after active surveillance and 87% in the group receiving active treatment, with no difference in OS. With a median follow up of 69 months, only 10 patients in the watch-and-wait group required active treatment [24]. Also, in a French multicenter study of 164 adult patients, OS did not differ between the group actively treated or observed. With a median relapse rate of 3 years, 50% of observed patients remained without treatment, and with inferior PFS. OS was equal in both groups [13]. In a prospective pediatric trial (NCT00107198), patients younger than 22 with stage IA completely resected were observed carefully. In a case of relapse, 3 cycles of doxorubicin, vincristine, cyclophosphamide and prednisone were administered. Of 52 patients after complete surgical excision, 13 relapsed at a median of 11.5 months. 5-year OS was 100% [19]. Upfront monotherapy with rituximab alone is associated with high response and relapse rates [12, 23]. In the prospective GHSG study, 28 patients with stage IA received 4 weekly doses of rituximab with an objective response rate (ORR) of 100% (85% CR) but 3-year PFS was 81.4% [25]. In another prospective phase II trial, 39 patients with recurrent or newly diagnosed NLPHL were treated with 4 weekly doses of rituximab followed by observation or 2 years of maintenance therapy. After 4 weeks of induction, ORR was 100% with CR of 67%. 5-year PFS for the rituximab-only arm was 39% whereas for rituximab with maintenance it was 58.9% [26]. However, the potential role of rituximab alone in induction treatment may be supported by the high rate of responses and no severe grade 3/4 toxicity. Anti-CD20 antibodies can be

considered individually as induction treatment for early stage NLPHL for patients in poor performance status with concomitant diseases.

Advanced disease

There have been no randomized trials directly comparing induction chemotherapy regimens, and the data is based on retrospective observations or phase II trials. The upfront use of anti-CD20 antibody is strongly recommended due to the consistent expression of that antigen on the LP cells surface. Therefore, the recommendation for ABVD alone in advanced disease may not be as relevant as it used to be. Still, the choice of chemotherapy which should be combined with antibody remains debatable. Regimens of CHOP, ABVD, CVP or bendamustine are taken into account. The BEACOPP protocol is not recommended widely outside the GHSG. RABVD consists of rituximab at a standard dose on day 1 and classical ABVD every 14 days of a 28-day cycle. In a short report, ORR was 100% with one PR out of six patients [27]. Fanale et al. [10] reported 27 patients with newly diagnosed NLPHL (16 patients with CS III/IV) who achieved a CR rate of 89%, ORR of 100 % after induction RCHOP. Median follow-up of the group was 6.7 years, and estimated 5-year PFS was 89% with no transformation event during the observation.

There is no strong evidence to support the use of immunochemotherapy regimens recommended for follicular lymphoma such as RCVP and R-Bendamustine. Published data shows very small groups with individual cases of advanced disease, often without anti-CD20 antibody [15, 16]. NLPHL with constant CD20 expression on the malignant cells, indolent nature, watch-and-wait periods, late relapses, and a risk of transformation follows the clinical course of follicular lymphoma. Histological growth patterns A and B are favorable factors in terms of outcome. Therefore, it would be very interesting to conduct a trial exploring the role of these regimens in the induction treatment of classical variant NLPHL.

Relapsed NLPHL

The treatment of relapsed or refractory NLPHL remains undefined. The management of refractory disease depends on several factors associated with the characteristics of the disease (localized or disseminated relapse, time of relapse, transformed), with the patient's status (age, general condition, concomitant diseases) and with the type of previous treatment. There are no prospective studies comparing different salvage strategies in refractory and relapsed NLPHL. Re-biopsy is necessary to distinguish NLPHL from non-malignant lymphadenopathy or transformed disease. Patients with negative biopsy results should undergo active surveillance. Biopsy-proven NLPHL relapses can be asymptomatic as recurrent indolent lymphomas. Therefore, active surveillance can be appropriate in particular cases.

Another option is monotherapy with rituximab followed (or not) by two years of maintenance treatment. Prolonged administration of rituximab may result in a longer PFS period compared to four doses of rituximab alone, but results from the single small study were not statistically significant [26]. Other preferences for refractory NLPHL are: radiotherapy alone for limited relapse, and systemic salvage chemotherapy with or without rituximab in advanced disease according to the guidelines for diffuse large B cell lymphomas.

For young patients with a disseminated and refractory (<1 year) relapse, AHCT should be considered first of all. In a retrospective analysis of 26 patients transplanted five years previously, event-free survival (EFS) was 69 and OS 76% [28]. Even better results were reported by the GHSG. Among 31 transplanted relapsed and refractory patients, 5-year PFS was 84.6 and OS 89.8% [29]. The use of rituximab plays an important role in salvage strategy containing AHCT. Akhtar et al. reported 5-year EFS of 76% in transplanted NLPHL; after rituximab salvage 100%, without rituximab 56% [30].

Transformed NLPHL

Upfront transformation should be treated identically to DLBCL. Consolidation with AHCT in the first line is debatable. In a relapse setting, there is no standard management established, and treatment strategies are determined individually.

Modern treatment approaches

The role of modern targeted approaches in NLPHL is undefined. Only small groups of patients or case reports can be presented to outline the new treatment directions for relapsed or refractory NLPHL. Radioimmunotherapy selectively delivers radiation from radionuclides to tumor cells. In one prospective study, murine anti-CD20 antibody radiolabeled with Yttrium-90 (ibritumomab tiuxetan) was used in the treatment of CD20 positive relapsed lymphomas (including three patients with NLPHL). The ORR was 88% including 65% complete metabolic response [31]. A case report of 2 NLPHL patients in first relapse after rituximab showed well tolerated treatment with ibritumomab tiuxetan with no relapse during seven years of observation [32]. The IRENO phase II trial is conducted by the German Study Group to evaluate the efficacy and safety of ibrutinib in patients with relapsed NLPHL (NCT02626884) [33].

Lenalidomide is the agent which can block directly tumor growth and modulate tumor microenvironment by stimulating cytotoxic T cells and NK cells.

Individual cases of NLPHL or T cell histiocyte-rich large B cell lymphomas successfully treated with lenalidomide with or without rituximab can be found [34, 35]. There is no data regarding the use of check point inhibition in NLPHL. PD-L1 expression on LP cells is heterogenous. On the other hand, PD-L1 is located on the bystander

histiocytes especially in variant histology pattern E [5]. Very likely, clinical trials with immune check inhibitors will be conducted.

Conclusions

NLPHL is a unique entity in between HL and indolent follicular lymphoma. Due to its rarity, no randomized multicenter trials have been performed so far to establish separate straightforward treatment guidelines. Data derived from single-arm studies, national registries, retrospective series and subgroup analysis of HL trials, confirm its excellent prognosis. Therefore, the treatment of NLPHL has become less aggressive over time. This is to reduce acute and late toxicity including cardio-pulmonary complications or secondary cancers, especially because NLPHL often occurs in children and young adults. New treatment strategies have focused on limiting radiation, adding anti-CD20 immunotherapy to chemotherapy, and careful use of active surveillance as an alternative to immediate or delayed treatment. The cooperation of large multidisciplinary diagnostic and therapeutic groups would be advisable to establish modern clear standards of NLPHL management and to develop new treatment strategies.

Author'scontributions

EP-K — sole author.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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