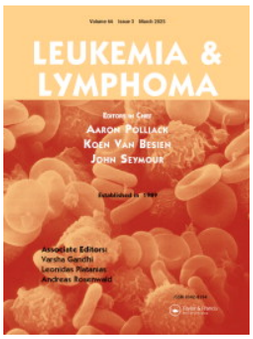

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LETTER TO THE EDITOR

Patient and care partner perspectives on treatment decision-making in nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL): a Global nLPHL One Working Group (GLOW) study

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Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare, generally indolent lymphoma affecting patients of all ages with risks for late relapse and transformation more than 20 years after initial diagnosis [1,2]. NLPHL remains understudied due to its rarity and the limited longitudinal clinical data needed to establish a standard of care treatment paradigm. NLPHL management has evolved from regimens utilized for classic Hodgkin lymphoma (cHL), but with wide variability globally [1,2]. There is no published research on patient and care partner (PaCP) needs, priorities, or goals after a diagnosis of NLPHL to inform shared decision-making given multiple NLPHL management options. Patient engagement and qualitative studies are vital in ensuring patient needs are addressed to achieve patient-centered care, to provide meaningful, patient-centered information about the benefits and risks of care options, and to enable future clinical research through participatory and co-design research methodologies [3,4].

The Global nLPHL One Working Group (GLOW) is exploring adapted treatment regimens for patients with NLPHL aimed at avoiding overtreatment and alignment with patient priorities based on advances in NLPHL risk stratification [1,5]. We conducted a qualitative study of patients diagnosed with NLPHL and care partners to understand perspectives about management options and to inform future clinical trials.

Adult individuals aged 18 and older reporting a diagnosis of NLPHL and care partners were eligible to participate. Participants were recruited by the study team and physicians within GLOW. The study team circulated an online registration form in English *via* the GLOW email listserv and Twitter for physicians to share with current and former patients and *via* NLPHL Facebook groups. PaCPs were asked to participate in one of three one-hour focus groups on Zoom. Registered participants were sent a calendar invitation and session reminders *via* email beforehand and were invited to submit written comments afterward.

Focus group sessions were moderated by one of two study team members (A.M. and V.M.C.) utilizing a semi-structured interview script and slide deck (Supplementary Materials). Each session was co-moderated by an oncologist with experience caring for patients with NLPHL (A.M. and J.E.F.). One or more other team member(s) took notes. The following 5 topics were discussed: 1) most important treatment priorities for patients with NLPHL; 2) perceived tradeoffs between different NLPHL treatment options; 3) information that PaCPs want from their care team when deciding between treatment options; 4) how symptoms and side effects should be assessed and discussed before, during, and after treatment; and 5) opinions regarding a prospective clinical trial design for early-stage NLPHL comparing different doses of radiation therapy (RT) against de-escalated chemoimmunotherapy (CIT) regimens. Each group was shown a visual of a trial schematic under consideration by GLOW. Each session was recorded on Zoom, and transcripts were saved utilizing Zoom's built-in automated transcription feature [6].

Rapid qualitative analysis of notes, transcriptions, and written feedback from participants was performed [7]. Two authors independently identified themes *via* inductive coding for each of the 5 topics [8]. After individual coding, the study team reviewed results, discussed discrepancies, and achieved consensus. The summary results were circulated to participants and to GLOW for review, refinement, and discussion. All session notes were de-identified, and Zoom recordings were deleted after coding. The study was determined as exempt by the Colorado Multiple Institutional Review Board.

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Thirty-six individuals registered for focus group participation, of which 10 participated in one of three virtual focus groups and/or provided written feedback; five identified as current patients, three as survivors, and two as care partners. Participants were aged 19–65 and 6 (60%) were male.

Key themes were identified within each of the five group discussion questions; additional themes emerged organically (Table 1).

Treatment priorities

Participants indicated that maximizing remission and long-term survival while minimizing side effects and preserving health-related quality of life (HRQoL) was the ideal prioritization of treatment goals. However, there was frustration and confusion regarding if NLPHL is truly curable; this distinction was felt to be important when weighing care strategies (treatment versus watchful waiting [WW], CIT versus RT). Obtaining second opinions from experts who see many patients with NLPHL was considered very important. Weighing opinions from different oncologists, given the lack of a standard of care approach for NLPHL, created anxiety. Patients treated for NLPHL as children or adolescents had unique perspectives given parental involvement in decision-making, with prioritization of immediate treatment over WW and of concerns surrounding long-term side effects and fertility.

Tradeoffs between different treatment options

Side effects and HRQoL were major considerations in care decisions. Several participants identified power and knowledge dynamics between physicians and patients as a barrier to understanding treatment tradeoffs. At times, patients' priorities conflicted with physician treatment recommendations, such as when physicians recommended more aggressive treatments with a higher likelihood of long-term remission despite patients preferring less toxic options; in these cases, patients sought oncologists favoring WW. Although some participants expressed comfort in knowing that treatment is not necessarily needed in patients without symptoms, others believed that mental and emotional well-being were particularly important in care discussions. In some cases, patients chose upfront treatment to avoid anxiety about symptoms during WW.

Preference for information provided by the care team

Most participants desired a concrete care recommendation from their oncologist that incorporated their own values and preferences (e.g. avoiding obvious swollen lymph nodes or preserving HRQoL). Second opinions from physicians with NLPHL expertise were considered important in obtaining up-to-date information. Participants requested patient-friendly NLPHL management guidelines, including guidelines on when treatment should start for patients on WW. Additionally, participants requested resources with data outlining benefits, short- and long-term risks and side effects, and symptom burden with each care strategy.

Symptom assessment and discussion during treatment

Participants indicated that a summary of new symptoms that might warrant treatment initiation and periodic surveys to check those symptoms would be helpful during WW. Patients requested open discussions regarding possible symptoms and side effects during WW and during treatment, as some believed NLPHL causes distinct symptoms beyond typical lymphoma-related "B" symptoms. Participants perceived there to be overreliance on lab testing, given that their bloodwork was usually normal. Short email or text surveys were believed to be helpful during treatment but should not supplant access to the care team.

Perspectives on early-stage clinical trial

When shown the clinical trial schematic including WW, RT, and CIT arms, participants reiterated that they wanted a concrete study arm recommendation from their oncologist. Participants had mixed reactions to randomization; further discussion indicated that providing patient-centered documentation explaining the rationale for each arm, for randomization, and for differing doses would be important in deciding between RT or CIT. Participants also requested summaries of anticipated symptoms and side effect profiles for each trial arm. Patients were open to symptom and side effects assessments before each trial visit as well as remote check-ins between visits.

Emerging themes

Additional themes arose organically. Participants expressed anxiety about the diagnostic certainty of NLPHL, given that several had been misdiagnosed with cHL. Patients indicated feeling "alone-ness" in their diagnosis, given the rarity of NLPHL and the limited experience of their care team in treating NLPHL. Participants were grateful to meet others with NLPHL during the focus groups. Participants expressed wanting to understand how disease stage guides treatment decisions, as stage III-IV NLPHL does not necessarily indicate high-risk disease. Lastly, some expressed confusion regarding the correct name for NLPHL given changes in the classification of NLPHL and the introduction of the term "nodular lymphocyte predominant B-cell lymphoma" (NLPBL) [9] among other terms used by their care team (e.g. "LP" and "Poppema.") Differing terms made it difficult to find patient-centered NLPHL resources.

Table 1. Summary of themes identified from each discussion topic.

Discussion topic	Key themes	Representative quotations
Most important treatment priorities for patients with NLPHL	• Confusion regarding "curability" of NLPHL • Desire to maximize remission and long-term survival while minimizing side effects and preserving quality of life • Unique perspectives of patients treated as children or adolescents	• "This is a rare disease and there isn't a lot of data, so I wonder if all of the treatments are truly palliative or if there really is a curative treatment." • "There is no set protocol, and it is all someone's best guess…That's scary." • "Side effects are a big priority."
How patients with NLPHL think about the tradeoffs between different treatment options	• Weighing chemoimmunotherapy vs. radiation therapy vs. watchful waiting • Importance of impact on mental health • Recognition of knowledge and power dynamic between patients and clinicians	• "Watch and wait is like being a ticking time bomb without a detonation time." • "Watch and wait is freaky when I have lumps everywhere." • "Mental health is a huge component." • "Is today the day when the enemy is going to come and attack?" • "Quality of life really drove my decision." • "I think more people are going to choose radiation. Chemotherapy *a priori* sucks." • "Living a life in watchful waiting mode is the pits."
The information that patients and caregivers want from their care team when deciding between treatment options	• Preference for physician to make definitive recommendation based on patient's values and preferences • Requests for concrete treatment guidelines as well as summaries of risks, benefits, and side effects of each care option to be provided to patients • Concern about general lack of data on NLPHL to confidently make care decisions and subsequent implications for values-based care decisions • Value in receiving second opinion from physician experienced in caring for NLPHL	• "When my doctor gave me options, it's like the CEO asking the janitor…I really hate that, you're the consultant that I paid to see, I'm gonna do whatever you want me to do." • "A doctor who is able to speak from experience instead of theory."
How symptoms and side effects should be assessed and discussed with the care team before, during, and after treatment	• Importance of recognizing symptoms other than lymphoma-specific "B" symptoms • Importance of brief symptom assessments, with opportunities to discuss those symptoms directly with the care team if requested	• "If physicians could be more accepting of symptoms that don't check off the boxes like B symptoms…because these symptoms, even if they aren't B symptoms, affect treatment decision-making." • "Concise questionnaires only for symptoms seen in NLPHL would be helpful to fill out on a text or email, but keep them short." • "If I'm having certain symptoms or side effects, I won't be in a place to fill out a survey to ask for help. I just want to ask my team what I need to do about these symptoms." • "An app would be great. You could fill in when it's happening, like symptoms in a migraine app. It helps also inform the patient because they can look back over time and see how bad it was or wasn't."
Opinions on GLOW early-stage clinical trial	• Some discomfort with randomization vs. belief that randomization brings comfort • Desire to have a clear recommendation from physician • Importance of providing information in ways the patient will understand	• "It feels freaky that it would be randomized, but it makes sense that this is how you do a clinical trial. My rational brain understands that this is good for the human race, to do this study, but my reptilian brain is weirded out by that. But the fate of my long term health being down to a randomly generated number is freaky." • "I think this would be overwhelming for me to make a decision…I would rather hear about both options and get a specific recommendation from my doctor." • "I'd rather have it randomized, to be honest, because I don't understand the difference between 20 and 30 Gy, and would just hope that both would work." • "I feel like I want the doctor to recommend one of the options; I wouldn't want to have to pick between two options." • "For anyone with a learning disorder in a high-stress situation, bullet points might not be great. There probably is not one solution for all. We need to think about what would work for young people; maybe written down wouldn't be best." • "I am a visual person; I would like to see it. A paper with bullet points would be good so I could write down notes, but it doesn't need to be exhaustive."
Emerging themes	• Anxiety around the diagnostic certainty of NLPHL • Feelings of "alone-ness" in diagnosis • Desire to know how the stage of the disease guides treatment • Confusion over the correct name for NLPHL and implications when searching for NLPHL resources	• "It's nice to see other people with this disease [on this Zoom]. I feel like the way the doctors have been framing it, I'm the only human in the universe with it." • "If he was early stage, the biggest question is what would be the advantage of treatment. Earlier treated and earlier remission, hopefully means cured." • "For NLPHL, rather than stage, should the treatment decision be based on how the cancer is affecting the daily life of the patient?"

Table 2. Opportunities to better serve patient and care partner needs in NLPHL care and research.

#	Category	Opportunity
1	Guidelines	Creation of consensus expert guidelines on the diagnosis and management of NLPHL from initial diagnosis through survivorship, including guidelines for relapse, refractory, and/or transformed NLPHL. These should include management guidelines for patients on active surveillance.
2	Patient care	Creation of written information and accompanying data tailored to: • *Oncologists* about NLPHL as a disease, management options (including active surveillance), and the risks and benefits of the various treatment modalities to help facilitate informed shared care decisions with patients and care partners. • *Patients and care partners* about NLPHL as a disease, management options (including watch and wait), and the risks and benefits of the various treatment modalities to help facilitate informed shared care decisions with the NLPHL care team. Additional brief synopses of available clinical trials, including the rationale for the trial and each trial arm, should be made available. These resources should be provided to patients and care partners in the form of preprinted paper handouts with space to take notes and should also be available online.
3	Patient care	Open and honest communication between patients, care partners, and health care teams about available literature regarding NLPHL and specific health concerns that patients may have. Attention should be given to the mental health and needs of patients and their care partners through their NLPHL journeys. Connection to cancer-specific support resources should be made as indicated.
4	Patient care	Development of a phone app for symptom tracking.
5	Patient resources	Improvement in the searchability and findability of NLPHL patient resources online, such as the creation of a unique NLPHL heading on lymphoma webpages (as opposed to solely as a subheading within classical Hodgkin lymphoma or non-Hodgkin lymphoma patient resource content).
6	Patient resources	Creation of peer support groups for patients diagnosed with NLPHL and their care partners.
7	Patient resources	Publication of videos online by experts about NLPHL and available clinical trials.
8	Research	Dedicated longitudinal studies of symptom variety, symptom burden, treatment-related side effects, and treatment tolerability in patients with NLPHL should be pursued.

This qualitative study assessed PaCP perspectives regarding care priorities and preferences in NLPHL, with focus group sessions indicating that a diagnosis of NLPHL is often a long, confusing, and isolating journey. As in interviews of patients with other chronic blood cancers and rare diseases [10–15], participants in our study expressed emotional distress (particularly regarding uncertainties associated with their diagnosis), "intuitive knowing" about their body and symptoms, and the importance of feeling heard by clinicians. Additional causes of distress pertained to delays and misdiagnoses during their diagnostic journey, varying opinions about treatment approaches from oncologists, lack of experience in caring for NLPHL, uniqueness of NLPHL as an rare and indolent lymphoma, isolated experiences living with NLPHL, lack of patient-centered resources, and challenges of clinical decision-making with limited data.

Our data reveal the importance of value-aligned shared decision-making in NLPHL and indicate several actionable goals to better meet PaCPs' physical and psychosocial needs (Table 2). These include NLPHL-specific decision support materials for PaCPs and medical professionals, diagnostic and management guidelines from diagnosis through survivorship, recommendations for supporting patients undergoing WW, and longitudinal studies of patient needs, symptoms, and HRQoL. As with patients with other indolent blood cancers, there is variability in patients' preferences and needs [14], and these may change over time. As such, and given PaCP concerns regarding the methodologic design of the early-phase clinical trial, we intend to integrate PaCPs directly into ongoing design of prospective GLOW clinical trials to enable robust integration of PaCP expertise into GLOW's research program.

The generalizability of these findings is limited due to the small sample size (albeit for a rare disease) as well as potential biases due to English language and online Zoom focus group requirements. Further, the lack of compensation for participants may have introduced additional socioeconomic barriers to participation. Nonetheless, the semi-structured nature of the sessions enabled detailed dialogue with and between PaCPs and established a foundation for future patient-partnered NLPHL research.

In conclusion, this study promotes the alignment of NLPHL research with PaCP priorities, presents qualitative data to inform NLPHL clinical trial design, and proposes strategies to improve PaCP counseling to address the anxiety and frustration experienced while living with NLPHL.

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