**Frontline management of nodular lymphocyte predominant Hodgkin lymphoma – a retrospective UK multicentre study**

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**Running short title:**

Frontline management of NLPHL

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Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a rare entity with an incidence of around 0.3 per 100,000 (Smith*, et al* 2015). With distinct morphological and immunophenotypical features, it differs from classical Hodgkin Lymphoma (cHL) clinically and biologically. The clinical course in NLPHL is generally indolent and prognosis favourable, especially for patients with early stage disease. NLPHL can transform into diffuse large B cell lymphoma, with reported rates of transformation varying in the literature from 3-14% (Al-Mansour*, et al* 2010, Farrell*, et al* 2011). However, deaths from NLPHL are uncommon and therefore late toxicity from treatment is an important factor to consider in determining the optimal management plan for these patients.

Approach to management is inconsistent given the rarity of this condition and the limited evidence base for optimal treatment. There are no randomised controlled trials and few prospective studies to compare different treatment approaches.

We performed a multicentre retrospective analysis aimed at determining the long-term outcomes of patients diagnosed with NLPHL in the modern era, with a particular focus on initial management approach and rates of high grade transformation (HGT). We pooled data from three UK sources: Haematological Malignancy Research Network (HMRN) (n=115; year of diagnoses: 2004-14), Nottingham Universities Hospitals NHS Trust, (n=48; 2001-7) and West of Scotland (n=70; 2004-13).

Analyses were conducted using standard methods in the statistical package Stata v15.1 (StataCorp 2017). Kaplan-Meier and Cox proportional hazard regression were used to estimate overall survival (OS) and progression-free survival (PFS) from time of diagnosis. PFS events were defined as disease progression requiring treatment for those initially on watch & wait, or if initially treated at diagnosis, time to relapse, transformation or death due to lymphoma. The Stata program Strel (v1.2.7) was used to estimate relative survival (RS) of the whole cohort with age and sex-specific background mortality rates obtained from national life tables (Spika D 2018).

233 patients with a histological diagnosis of NLPHL were included with median follow up of 8.4 years. The majority of patients were male (77.3%), had early stage disease (76.7%) and B-symptoms were uncommon (10.9%). Median age at diagnosis was 43 years, with 12/233 (5%) patients aged <16 years. The 5-year OS of the 233 patients was 97.0% (95%CI:93.8-98.6).

Table 1 outlines patient characteristics and approaches to frontline management. In total, 9/30 (30%) patients suffered disease progression after ‘watch and wait’ (W&W) (1 patient with HGT at time of progression). 23/203 (11.3%) relapsed following frontline treatment (chemotherapy, radiotherapy or both) – ten of these patients had HGT at relapse.

Seven (3%) patients died within 5 years of diagnosis; four had been treated with chemotherapy+/-radiotherapy. Two of these patients died of lymphoma with one patient having a HGT. HGT occurred in a total of fourteen patients (6.0%) – eleven as a first event following frontline management and three patients whose disease had previously relapsed. Those suffering HGT had a 5-year OS of 92.9% (95%CI:59.1-99.0) with median time from diagnosis to disease transformation of 4.7 years (range 0.2 – 13.7).

Of the 178 patients who presented with early stage disease (stage I/II), 19 (10.7%) were managed by W&W and 115 (64.6%) by radiotherapy alone. 44 (24.7%) were treated with chemotherapy, including 12 who also received radiotherapy. Those patients managed by W&W had 5-year PFS of 71.5% and OS 96.7%.

Fifty-four patients (23.3%) presented with advanced stage disease, the majority were treated with chemotherapy (74.1%). Eleven patients (20.4%) were initially managed by W&W with excellent outcomes (5-year PFS 70.0%/OS 100%) – all were aged >18 years and had stage III disease. Overall, for those that received chemotherapy, ABVD or R-CHOP were the most common regimens, with CVP+/-R mainly reserved for younger patients.

The survival outcomes and rates of HGT were similar in our study to those reported in a previous, single centre, analysis of 222 patients (Kenderian*, et al* 2016), confirming that NLPHL predominantly affects younger adults, more commonly men, with the majority having absent B symptoms and following an indolent course with excellent long term outcomes. The occurrence of HGT is low – 6% in our study – and is highly treatable with good long term outcomes.

A watch and wait approach yields excellent results in early stage patients but also in some advanced stage patients with asymptomatic, indolent disease. For early stage patients, complete excision at diagnosis can be curative – a limitation of our study is that data for those treated with complete excision were not available. For the majority of early stage patients not treated by complete surgical excision, radiotherapy alone is a very acceptable treatment and avoids toxicities related to chemotherapy.

For advanced stage patients, current BSH guidelines (McKay*, et al* 2016) advise treatment with rituximab in combination with chemotherapy. As this was an observational study with excellent outcomes across all treatment groups, we cannot determine if there were any differences in outcome with different chemotherapy regimes. With the relatively small number of patients receiving rituximab, and variation in chemotherapy backbone, it is not possible to draw conclusions on its influence on patient outcome.

Management of NLPHL is variable across the world with many centres continuing to offer anthracycline-containing regimes e.g. ABVD, RCHOP (Fanale*, et al* 2017). However, we believe that our data supports recent evidence (Borchmann*, et al* 2019) to suggest that a stepwise approach to management in terms of intensity is advisable, with many patients having excellent outcomes following ‘watch and wait’ as an initial management strategy and those relapsing following initial therapy responding well to further treatment. Low intensity immuno-chemotherapy e.g. R-CVP is recommended to reduce long term toxicities with more intensive regimes reserved for those with suspected HGT or other concerning features.

The main strength of our study is the collaborative, multicenter approach allowing analysis of a large number of cases treated in the chemoimmunotherapy era. We acknowledge that the retrospective nature of the study and variation in treatment approaches does not allow any definitive conclusion to be drawn on optimum management of NLPHL. International multi-centre collaboration will be required to establish prospective trials to assess the ideal management of this rare disease.

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**Authorship**

**Contribution:**

PM and CB conceived the study; MRW, KH, ML, RP and MB collected data; TB, AS and ER analyzed data and created the table and figure; MRW and KH wrote the manuscript; all authors contributed to and approved the final version of the manuscript.

**Conflict-of-interest disclosure:**

The authors declare no competing financial interests.

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**Table 1**

**Baseline characteristics by frontline management**

|  |  |  |
| --- | --- | --- |
|  |  | **Frontline management n (%)** |
|  | **All****Patients****n (%)** | **Watch & Wait** | **Radio-therapy****Only** | **Chemotherapy +/- radiotherapy** |
|  |
|  | **N=233** | **N=30** | **N=119** | **N=84** |
|  |  |  |  | **Total** | **ABVD****N=31** | **R-CHOP****N=29** | **CVP +/-R1****N=15** | **Other2****N=9** |
| **Sex:** |  |  |  |  |  |  |  |  |
| **Males**  | 180 (77.3) | 18 (60.0) | 90 (75.6) | 72 (85.7) | 25 (80.6) | 27 (93.1) | 12 (80.0) | 8 (88.9) |
| **Females** | 53 (22.7) | 12 (40.0) | 29 (24.4) | 12 (14.3) | 6 (19.4) | 2 (6.9) | 3 (20.0) | 1 (11.1) |
|  |  |  |  |  |  |  |  |  |
| **Median age at diagnosis (IQR) years** | 43.0(27.6 - 57.1) | 56.4(34.6 - 65.5) | 41.3(27.1 - 57.1) | 41.1(27.2 - 53.6) | 44.1(30.0 - 51.7) | 44.0(33.0 - 53.3) | 16.0(12.0 - 29.5) | 62.0(36.0 - 66.0) |
|  |  |  |  |  |  |  |  |  |
| **Median follow-up (IQR) years** | 8.4 (8.0 - 9.0) | 7.2 (5.3 - 9.9) | 8.6 (7.9 - 9.3) | 8.5 (7.8 - 9.2) | 9.8 (8.5 - 10.8) | 8.1 (6.4 - 9.0) | 5.0 (2.7 - 7.8) | 9.0 (5.4 - .) |
|  |  |  |  |  |  |  |  |  |
| **Stage at diagnosis:** |  |  |  |  |  |  |  |  |
| **I&II** | 178 (76.7) | 19 (65.5) | 115 (96.6) | 44 (52.4) | 15 (48.4) | 13 (44.8) | 11 (73.3) | 5 (55.6) |
| **III&IV** | 54 (23.3) | 10 (34.5) | 4 (3.4) | 40 (47.6) | 16 (51.6) | 16 (55.2) | 4 (26.7) | 4 (44.4) |
| **CT/PET Scan not done**  | 1 | 1 | - | - | - | - | - | - |
|  |  |  |  |  |  |  |  |  |
| **B symptoms** | 25 (10.8) | 2 (6.7) | 5 (4.2) | 18 (21.7) | 6 (19.4) | 8 (27.6) | 1 (6.7) | 3 (37.5) |
|  |  |  |  |  |  |  |  |  |
| **Transformation to DLBCL** | 14 (6.0) | 1 (3.3) | 6 (5.0) | 7 (8.3) | 4 (12.9) | 2 (6.9) | - | 1 (11.1) |
|  |  |  |  |  |  |  |  |  |
| **5-year overall survival:**  |  |  |  |  |  |  |  |  |
| **Deaths**  | 7 (3.0) | 1 (3.2) | 2 (1.7) | 4 (4.8) | 1 (3.2) | 2  (6.9) | - | 1 (11.1) |
| **%** | 97.0 | 96.7 | 98.3 | 95.2 | 96.8 | 93.1 | 100 | 88.9 |

1 five patients received rituximab
2 four patients rituximab only, two ChlVPP, two OEPA, one VAPEC-B

IQR (Interquartile range), DLBCL= Diffuse large B-cell lymphoma

**Figure 1 Legend**

**Progression free, relative and overall survival and cumulative incidence of transformation with death as a competing risk**

