Advanced stage nodular lymphocyte predominant Hodgkin lymphoma in children and adolescents: clinical characteristics and treatment outcome - A report from the SFCE & CCLG groups

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Summary

Advanced stage nodular lymphocyte predominant Hodgkin lymphoma [nLPHL] is extremely rare in children and as a consequence, optimal treatment for this group of patients has not been established. Here we retrospectively evaluated the treatments and treatment outcomes of 41 of our patients from the United Kingdom and France with advanced stage nLPHL. Most patients received chemotherapy, some with the addition of the anti CD 20 antibody rituximab or radiotherapy. Chemotherapy regimens were diverse and followed either classical Hodgkin lymphoma [cHL] or B non-Hodgkin lymphoma [NHL] protocols. All 41 patients achieved a complete remission with first line treatment and 40 patients are alive and well in remission. Eight patients subsequently relapsed and 1 patient died of secondary cancer [9 PFS events]. The median time to progression for those who progressed was 21 months [5.9-73.8]. The median time since last diagnosis is 87.3 months [8.44-179.20]. Thirty- six [90%], 30 [75%] and 27 [68%] patients have been in remission for more than 12, 24 and 36 months respectively. Overall, the use of rituximab combined with multi-agent chemotherapy as first line treatment seems to be a reasonable therapeutic option.

Key words: nodular Lymphocyte Predominant Hodgkin Lymphoma, children & adolescents, advanced stage, rituximab, chemotherapy,

Running title: Advanced stage nodular lymphocyte predominant Hodgkin lymphoma in children and adolescents

Introduction

Nodular lymphocyte predominant Hodgkin lymphoma [nLPHL] comprises approximately 10% of Hodgkin's lymphoma in children and adolescents [**McKay et al 2015, Shankar et al 2015, Hall et al 2007**]. Whilst around 80% will present with early stage disease [stages I and II] without mediastinal lymphadenopathy, B symptoms or extra nodal involvement, 15-20% will have advanced stage disease at first diagnosis [**Shankar et al 2012**]. Whereas early stage nLPHL is an indolent lymphoma, advanced stage disease in adults has been reported as a biologically aggressive lymphoma with lower treatment response rates and poorer overall survival outcome [**Gerber et al 2015**, **King et al 2015**, **Xing et al 2014].**

Although current treatment approaches used for children and adolescents with advanced stage nLPHL are broadly similar to those used for advanced stage classical Hodgkin lymphoma [cHL] [**Mauz Korholz et al 2015, Dorffel et al 2013**, **Shankar et al 2012, Olson et al 2008**], these may not represent optimal therapy. Because of the dearth of information available on treatment outcomes in this rare patient group, there is no consensus regarding the optimal therapy for children and adolescents with advanced stage nLPHL.

This Anglo-French report is the largest cohort ever published and seeks to initiate a dialogue on how this group of patients can best be managed using retrospectively gathered information on treatment outcomes in forty-one children and adolescents with advanced stage nLPHL.

Patients and Methods

Forty-one patients up to their 19th birthday diagnosed with advanced stage nLPHL [clinical stage IIB, III & IV] between May 1998 and March 2015 [UK; n= 19 and France, n= 22] are the subjects of this report.

Data collection

In the United Kingdom, anonymized patient data [basic demographic information, treatment administered and treatment response] were retrospectively collected from the treating physicians through the Children's Cancer and Leukaemia Group [CCLG] audit of children and adolescents with advanced stage nLPHL. Consent for treatment, including collection of anonymized patient data, was obtained from patients and or their parents / guardians according to the prevailing institutional and ethical committee guidelines. The relevant anonymized French data was retrieved from the French registry of paediatric cancer and was checked for accuracy by each centre of the Société Francaise de lute contre le Cancer et les leucémies de I'enfant et de I'adolescent [SFCE]. Approval for collection of data was secured from French patients and or their parents/guardians in accordance to the local ethical and institutional guidelines in France.

Staging procedures

Staging at diagnosis generally included clinical history, physical examination, chest X-ray, computerised tomography and /or magnetic resonance imaging of neck, chest, abdomen and pelvis and bone marrow aspiration & trephine biopsies. While FDG PET scan was not a standard investigation for diagnostic staging until around 2006, a proportion of patients in both the UK and France underwent FDG PET scans as part of their staging investigations. There was no central review of imaging in either the UK or in France. Technetium-99m isotope bone scans were only carried out if the patient had symptoms of bone pain or had documented evidence of liver and or lung involvement. Where possible, [i.e. if peripheral lymph nodes or bone marrow were involved] relapse was confirmed by a biopsy, but when this was not possible, unequivocal new radiological lesions were considered as acceptable proof of recurrent disease in the absence of another plausible explanation.

Histology

In both nations, all cases were reviewed by specialist expert haematopathologists using a combination of haematoxylin and eosin (H&E) staining and immunohistochemistry to confirm the diagnosis of nLPHL and to exclude cHL and diffuse large B cell lymphoma (DLBCL). Immunohistochemistry was carried out using a panel of antibodies that included CD20, CD79a, CD3, CD10, bcl-6, CD21, CD30, CD15, EMA, OCT2, and PD1 or CD57. In the UK, additional assessment was performed in 10 cases to further classify the disease according to the histological variants as described by [**Fan et al 2003**].

Treatment strategy at diagnosis

As there was no standardized or consensus chemotherapy protocol for children with advanced stage nLPHL, a diverse combination of chemotherapy regimens were used; some with the addition of rituximab.

Some patients had involved field radiotherapy [IFRT] in addition to chemotherapy in accordance with the standards at the individual treating paediatric oncology centres.

Response criteria

Complete response [CR] was defined as disappearance of all disease related clinical symptoms and complete radiological resolution of all measurable disease. Partial response [PR] was defined as shrinkage of measurable disease that was 50% or greater reduction in any one axis. Poor response was defined as disease progression [new lesions or clear progression of pre-existing lesions] during or response less than PR to primary therapy [**Cheson et al 2014**].

Follow-up after first line treatment

Post treatment follow-up strategy was variable and in accordance with the treating centre's standard practice. The first follow-up visit was usually around 6-8 weeks after completion of treatment, followed by clinical evaluations at 3 to 4 monthly intervals during the first year after treatment and at 4-6 monthly intervals during the second and third years after treatment. As there were no recommended timelines for interval imaging during follow-up surveillance, this

was variable and dependent on the practice at the treating centre. In general, imaging was normally only undertaken in case of suspected relapse or disease progression. PET imaging was not routinely used to assess treatment response.

Statistical analyses

Descriptive statistics were used for most analyses. Kaplan-Meier survival analysis was used to assess progression free survival [PFS]. PFS times were calculated from diagnosis until progression or death [which ever came first]. Patients who were alive and progression free were censored at the last date seen. The time since last diagnosis was calculated from the last diagnosis [initial or relapse] until the date last seen. The patient who died of secondary malignancy was excluded. Differences in time to progression between groups were compared using the log rank test with $p<0.05$ considered statistically significant. All analyses were performed using STATA version 14.0 [**STATA Corp, Texas**].

Results

Baseline patient characteristics

A total of forty-one patients are included in this report. The demographics and disease characteristics at initial diagnosis of these 41 patients are shown in **table 1**. The median age of the cohort was 14 years [range, 4- 18 years]. B symptoms at diagnosis were documented in only 6 [15%]. The majority of patients had stage III disease. Sites of involvement in patients with stage IV disease at presentation included the lungs, liver and bone/bone marrow.

Variant histology

Categorization of nLPHL histology into typical or variant histology according to the Fan et al classification was only documented in the later UK cohort of 10 patients. Of these 10 patients, 9 had typical nLPHL and 1 showed variant pattern "E" histology [diffuse with a T-cell-rich background (TCRBCL or DLBCL-like)].

Imaging with FDG PET

While thirty-one patients had FDG PET as part of their diagnostic staging, only 12 had PET as part of their response assessment at the end of treatment. In the 12 patients who had PET at the end of treatment, all responses were primarily based on the PET result. There is no information available on the concordance between conventional cross sectional imaging i.e. CT or MRI and PET scans either at diagnostic staging or response assessment at the end of treatment.

Treatment

Patients were most commonly treated with chemotherapy alone [n=20]. Chemotherapy regimens used were variable; the most frequently used were ABVD/ChLVPP [n=7] OEPA/COPP or COPDAC [n=5] followed by CVP [n=3]. Twelve patients also received rituximab along with chemotherapy; the most common rituximab plus chemotherapy regimens were R-CHOP [n=5] and R-ABVD [n=3]. Six patients received a combination of IFRT and chemotherapy alone [n=5] or chemotherapy plus rituximab [n=1]. One patient received rituximab monotherapy while two patients had lymph node excision biopsy as the only form of treatment. **Table 2** and **figure 1** show the first line treatments used in these patients.

Treatment outcome and first remission

All 41 patients achieved a complete response to first line therapy, 8 patients subsequently relapsed and 1 patient died [9 PFS events]. The median follow up for those who had not progressed or died was 81.8 months [8.4 -179.2 months]. While the median time to progression for the entire cohort has not been reached, [**figure 2**] for those who had disease progression, this occurred at a median time of 21.0 months [5.9 -73.8 months]. One patient who had been progression free for 49 months after treatment for advanced stage nLPHL died of refractory secondary Ewing's sarcoma.

Treatment outcome according to treatment modalities [figure 1]

1. Combination chemotherapy

Twenty patients received chemotherapy alone as their first line treatment. While all 20 patients achieved a CR, 3 patients subsequently relapsed. These relapses occurred at 5.9, 6.6 and 9.6 months respectively. Two of the three patients received IFRT as part of their salvage treatment at relapse and one patient also received autologous stem cell transplantation [ASCT]**.** All 20 patients are either in first [n=17] or second [n=3] remission with a median of 99.1 months [range; 18.5-143.5] since their most recent diagnosis.

2. Combination chemotherapy with rituximab

Twelve patients received rituximab with chemotherapy as their first line treatment. R-CHOP [n=5] and R-ABVD [n=3] were the most common regimens used in this group. All 12 achieved a first CR but one patient subsequently relapsed and achieved a second CR with prolonged single agent rituximab alone. One patient died of secondary Ewing' sarcoma and the remaining 11 are currently in remission with a median follow up of 47.9 months [8.4-148.4] since their most recent diagnosis.

3. Chemotherapy plus radiotherapy

First line treatment in 5 patients consisted of chemotherapy [MOPP-ABVD; n=3 & OEPA-COPDAC; n=2] combined with IFRT. While all achieved a CR, three patients

subsequently relapsed and achieved a second complete remission. However, 2 experienced a second relapse and received further chemotherapy with rituximab followed by ASCT. All 5 patients are currently in remission with a median of follow-up times of 31.4, 109.1, 128.4 and 130.7 months since their last diagnosis.

4. Other treatment programs

Four children received varied treatments that included surgery alone [n=2], rituximab alone [n=1] and combination chemotherapy with rituximab and IFRT [n=1]. While all achieved a CR, one patient treated with rituximab alone relapsed. This patient was subsequently salvaged with chemotherapy plus 20Gy IFRT. All 4 remain well and in remission with median follow-up times of 17.5, 28.3, 77.9 and 118.1 months since their last diagnosis.

Current status

Eight patients relapsed and all have achieved a second complete remission. However, two of these patients had a second relapse and received ASCT as consolidation of the third CR. Treatment at relapse was diverse but 4 of 8 patients received rituximab alone at relapse [**table 3 and figure 1**].

Survival

Forty patients are alive and well**,** no patient has died from advanced nLPHL**.** The one death was due to secondary Ewing's sarcoma that occurred during first remission.

Time since last relapse

The median time since last diagnosis was 87.3 months [8.44 -179. 20] in all patients. Thirty-six [90%], 30 [75%] and 27 [68%] patients have been in remission for more than 12, 24 and 36 months respectively.

Risk factors for relapse

Baseline demographics and first line therapy of the patients who relapsed can be seen in table 4. Although all the relapses were in male patients [0/7 female; 8/34 male, p=0.16] and a larger proportion with B symptoms relapsed (4/34 without

symptoms and 4/6 with symptoms, p=0.0004) few conclusions can be drawn because of the small numbers and heterogeneous first line treatments [**table 4**].

Discussion

To our knowledge, there have been no publications on children and adolescents with advanced stage nLPHL.

Similar to previous reports in children with early stage nLPHL [**Shankar et al 2012, Murphy et al 2003, Sandoval et al 2002**], males predominate in our cohort. Bone/bone marrow and lung involvement were the most common sites of extra-nodal involvement. Although information on variant histology was not available for all patients, 1 of the 10 [10%] assessable patients had variant histology. Patients with variant nLPHL are known to present with higher stage disease at diagnosis [**Shankar et al 2015, Shet et al 2015, Fan et al 2003**]. Previous published reports have shown that males have a higher risk of relapse or disease progression [**Xing et al 2014, Hartmann S et al 2013**], a trend we also noted; with all relapses occurring in male patients alone [0/7 female; 8/34 male] although this was not statistically significant [p=0.16].

It is said that patients with nLPHL have a tendency for multiple and late relapses [**Diehl et al 1999, Hawkes et al 2012, Jackson et al 2010, Farrell et al 2011, Chera et al 2007**]. While only 2 patients in our cohort had a second relapse in it is possible that further recurrences may occur in the future.

While FDG-PET has a well-established role in the early treatment response assessment in cHL, its use as a predictive therapeutic tool via response-adapted therapy is less certain in nLPHL as there is a significant difference in FDG/glucose uptake between nLPHL and cHL [**Hutchings et al 2006**]. Three patients who had complete metabolic response on FDG PET at the end of treatment relapsed. In fact, an open international collaborative trial [EuroNet PHL LP1] for children with early stage nLPHL specifically dissuades clinicians from using FDG PET for response assessment at the end of chemotherapy due to high false positive rates.

There has been no development or transformation to secondary aggressive non-Hodgkin lymphoma in our cohort so far, although again this may happen with further follow-up in the future. Published literature of a series of 42 adult patients with advanced stage nLPHL where the majority were treated with ABVD like chemotherapy] report a cumulative risk of transformation of 24% at 15 years [**Xing et al 2014**].

It would appear from our cohort of patients, adopting either a cHL or B-cell non - Hodgkin lymphoma is effective. All 20 patients who were treated with chemotherapy alone achieved CR irrespective of the chemotherapy regimen used. However, the 3 patients who experienced a relapse were treated with chemotherapy protocols used in cHL [OEPA-COPP or OEPA/COPDAC]. There is no consensus on the optimal chemotherapy regimen for children or adults with advanced stage nLPHL [**Gaelle R et al 2014, Bose et al 2011; Eichenauer et al 2011].** Treatment recommendations from co-operative groups such as the European Society of Medical Oncology, the National Comprehensive Cancer Network and the UK Task Force guidelines for all ages include a variety of strategies; cHL and NHL strategies with or without rituximab [**McKay et al 2015, Hoppe et al 2012, Eichenauer et al 2011**].

There are a few reports that might persuade clinicians to use or avoid certain strategies over others including published studies in adults suggesting chemotherapy regimens with an alkylator spine are superior in nLPHL [**Canellos et al 2010, van Grotel et al 2006**] or that ABVD chemotherapy in adults with advanced stage nLPHL led to an increased incidence of secondary aggressive lymphoma resulting in inferior progression free survival [**Xing et al 2014, Ames et al 2015**]. However, it is significant to note that in our small cohort, alkylator based chemotherapy regimens were used in all 20 patients in the combination chemotherapy alone group.

It is likely that children and adolescents with stage IIIA NLPHL such as those with peripheral nodal disease i.e. cervical, axillary and external iliac or inguino-femoral lymphadenopathy have a similar overall outcome as those with stage IIA NLPHL [**Sandoval et al 2002**] and may not require intensive chemotherapy. In this group of patients R-CVP would be a reasonable treatment option [**McKay et al 2015**].

Rituximab combined with CHOP chemotherapy was an effective treatment approach in adult patients with advanced stage nLPHL [**Fanale et al 2010**]. A few other studies have similarly shown a clear therapeutic benefit of combining

rituximab with chemotherapy in patients with refractory or relapsed nLPHL [Shankar et al 2016, **Mocikova et al 2015, Lazarovici et al 2015, Advani et al 2014**]. The relapse rate in the chemotherapy only group in our cohort compared to the rituximab plus chemotherapy group was nearly double [15%; 3/20 vs. 8.3%; 1/12]. However as our data is limited, non-randomized and retrospective, we can only speculate that the addition of rituximab is likely to improve PFS.

It is possible that in the absence of routine surveillance scans during follow up, an asymptomatic relapse could have occurred several months before the clinical diagnosis of recurrent disease and thus, shortening the time to relapse or even "inflating" the PFS rates in our cohort of patients [if further undetected relapses have occurred]. However, patients with advanced central disease are likely to receive the same follow up as patients with cHL. Likewise any suggestion of clinical relapse noted by clinicians would prompt appropriate scanning.

Mono-therapy with rituximab for patients with advanced stage disease either at diagnosis or after relapse cannot be recommended as curative treatment in view of the inferior PFS with this strategy when compared to combining rituximab with chemotherapy [**Advani et al 2015**]. However, 2 of the 4 patients in our cohort who received single agent rituximab at relapse, derived some benefit as they remain in continuous second remission [10 and 131 months since relapse].

The rationale for using IFRT in addition to chemotherapy in 6 patients is unclear as the decision was not based on the presence of bulky disease at diagnosis or early treatment response assessment scan as these were not performed routinely in this cohort of patients. All 6 had stage III nLPHL and none had B symptoms. The role of IFRT as consolidation of first-line therapy in the management of patients with advanced stage nLPHL is controversial in children with nLPHL with considerable differences in practice across different treatment centres. However, as emerging data give support to the use of consolidative IFRT in patients with advanced stage DLBCL [**Specht L 2016**], there may be a role for consolidative IFRT in the management of patients with advanced stage nLPHL.

While ASCT as first line treatment for patients with advanced stage disease cannot be recommended, it is a reasonable therapeutic option for those with relapsed disease [**Akhtar et al 2016, Karuturi et al 2013**]. In our cohort, one patient received ASCT at first relapse and two at second relapse.

Even though the overall survival of our cohort is excellent [OS =98%], 8 patients relapsed once and 2 had a second relapse. Their overall treatment burden was considerably higher and it is therefore critical to balance the frontline treatment strategy against treatment related toxicities [acute and late] and the total burden of treatment [primary therapy and relapse treatment].

In summary, our data suggest that children and adolescents with advanced stage nLPHL have a very good outcome but should be treated with an appropriately weighted program of treatment intensity. Although this is the largest series of children with advanced stage nLPHL, the numbers are still small and, the non-randomized data and heterogeneity of treatment received [including ASCT] limits us from producing any evidence based guidelines on treatment. However we would make the following suggestions for this group of patients:

1. The use of rituximab combined with multi-agent alkylator containing chemotherapy such as CHOP i.e. R-CHOP as first line treatment in this group of patients seems a reasonable therapeutic option.
2. It is likely that children and adolescents with stage IIIA NLPHL such as those with peripheral nodal disease i.e. cervical, axillary and external iliac or inguino-femoral lymphadenopathy have a similar overall outcome as those with stage IIA NLPHL and may not require intensive chemotherapy

3. While residual FDG positivity at the end of treatment indicates presence of residual viable disease in cHL; similar criteria may not be applied for nLPHL where FDG uptake differs [**Hutchings et al 2006**] and hence, using FDG PET response to guide treatment intensification is inadvisable in patients with NLPHL.

4. Whether addition of IFRT to chemotherapy in this group of patients improves the survival outcome is debatable but using limited fields and radiation dose, it is not unreasonable if there is clear clinical evidence of poor response to frontline therapy or at relapse if IFRT was not used in primary treatment.
5. Monotherapy with rituximab either at diagnosis or relapse cannot be recommended as a curative modality
6. Considering the rarity of this disease, only an international trial will allow collection of disease and treatment specific characteristics that will enable the design of the optimal management approach for advanced stage nLPHL

Aside from inherent limitations of any retrospective report, the small size of our cohort restricts further definitive conclusions.

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Contribution of authors

AGS and JLP: conceived the study, analysed the data and wrote the paper

JH, GR, SG: contributed to the data management and analysis

AK: analysed the data and provided the statistical input for the paper

ADR: provided central review for all pathology samples in the United Kingdom and contributed to the writing of the manuscript

SB: provided central review for all pathology samples in France

KF, TL, AL: analysed the data and contributed to the writing of the paper

SA, CS, SH, NA: provided detailed clinical data [France]

GWH: contributed to the writing of the manuscript

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