Case Report

Minimising chemotherapy while optimising immune therapy for paediatric nodular lymphocyte-predominant Hodgkin’s lymphoma

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Abstract

Nodular lymphocyte-predominant Hodgkin’s lymphoma (NLPHL) is a rare but distinct subtype of Hodgkin’s lymphoma (HL) that carries a better prognosis than classical Hodgkin’s lymphoma. Historically, both subtypes of Hodgkin’s lymphomas (classical HL and NLPHL) have been grouped together and treated as classical Hodgkin’s lymphoma. Recent studies have questioned this approach and have called for an alternative method due to expected severe long-term adverse events. We report two cases of NLPHL that were successfully treated with reduced chemotherapy cycles, as well as rituximab, in the form of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone).

Keywords: Chemotherapy; Children; Hodgkin’s lymphoma; Lymphoma; Rituximab

Introduction

Paediatric nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is an uncommon subtype of Hodgkin lymphoma (HL), accounting for approximately 10% of HL cases. It demonstrates a male predominance, and affected children usually present with localised non-bulky disease and only rarely with advanced-stage disease.1-4 In contrast to the classical HL, NLPHL is characterised clinically by an indolent course and pathologically by CD20-positive lymphocyte-predominant (LP) cells.1,2 Such unique characteristics have prompted investigators to use different treatment approaches (targeted immune therapy) than those used for classical HL.

Until recently, most NLPHL patients have been managed similarly to classical HL patients. Although the current treatment approach for classical HL cures most children with HL, many are expected to experience serious long-term adverse
events, such as secondary cancers and late cardiovascular disease. Optimising the balance between the cure rate and long-term complications, i.e. curing patients with minimal to no side effects, remains a significant challenge for paediatric hematologists and oncologists. A standard treatment regimen for the treatment of NLPHL has yet to be established.

The current contemporary treatment approach for HL among paediatric cancer consortiums is utilising risk-adapted (i.e. treat according to the stage of disease) and response-based therapy (i.e. tailor therapy according to the initial response). Nevertheless, the actual chemotherapy (drugs, doses, and cycles) and radiotherapy (when, where, and dose) regimens are yet to be determined in randomised clinical trials.

One attractive potential adult regimen for NLPHL is known as R-CHOP, representing a combination of immunotherapy (rituximab) with chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone). Such a regimen has demonstrated high efficacy in treating NLPHL with an acceptable profile of adverse events. A dose reduction in chemotherapy (CHOP) yet providing immunotherapy powered by the addition of rituximab may decrease long-term adverse events while maintaining the curative effect. Adopting such a regimen for children with NLPHL may represent a “sweet spot” where many children can be cured and have long lives without compromised health. Here we report two cases that were successfully treated using a standard unified protocol (R-CHOP ×3).

Case report

Case #1

A previously healthy 7-year-old boy presented with a 4-month history of bilateral neck lymphadenopathy. The largest lymph node, located on the right side of the neck, measured 2 × 3 cm. He was otherwise well and had no B symptoms (fever, weight loss, or night sweats). A biopsy of the lymph node (LN) revealed the classic features of NLPHL with characteristic positivity for CD20, CD79, BCL6, and PAX5, and focal positivity for LCA and EMA.

Subsequently, the boy underwent a staging workup (neck, chest, and abdominal computed tomography [CT]) that confirmed bilateral cervical lymphadenopathy; however, no other abnormal LNs were identified. A positron emission tomography scan could not be performed at our institution due to the chronicity of the LN enlargement, an LN biopsy was performed. The resected LN revealed classic features of NLPHL (partial architectural effacement of the LN, nodular formation, and many sizeable atypical popcorn cells that were positive for CD20, CD45/LCA, and PAX5). We performed a staging workup (pan CT) that was positive for large right cervical and supraclavicular LNs. He had stage IIA NLPHL and was managed with R-CHOP ×3. No significant toxicities were encountered apart from febrile neutropenia and mucositis. The end-of-therapy evaluation showed a CR, and he has remained disease-free until now (2.5 years later).

Case #2

A 5-year-old male patient who was previously healthy presented with a 3-month history of right neck swelling; he was otherwise well with no B symptoms. There was right cervical and supraclavicular LN enlargement on physical examination, with the largest node measuring 2 × 2 cm. The rest of the examination was unremarkable. Laboratory investigations were completely normal apart from mild elevation of the lactate dehydrogenase (LDH) level at 255 U/L.

Due to the chronicity of the LN enlargement, an LN biopsy was performed. The resected LN revealed classic features of NLPHL (partial architectural effacement of the LN, nodular formation, and many sizeable atypical popcorn cells that were positive for CD20, CD45/LCA, and PAX5). We performed a staging workup (pan CT) that was positive for large right cervical and supraclavicular LNs. He had stage IIA NLPHL and was managed with R-CHOP ×3. No significant toxicities were encountered apart from febrile neutropenia and mucositis. The end-of-therapy evaluation showed a CR, and he has remained disease-free until now (2.5 years later).

Discussion

This is the first case series to report the use of R-CHOP in paediatric NLPHL. A literature review of the published reports in PubMed Central yielded no other reports of R-CHOP use in children with NLPHL except a single case report by Stier et al. in 2015. Historically, the majority of children with NLPHL have been cured using a treatment protocol intended for classical HL. Although it appears to be a beneficial approach, it carries significant long-term risks and entails potential treatment-related complications. A growing body of literature indicates that NLPHL is considered a distinct and more indolent disease than classical HL that requires different management.

It is noteworthy that NLPHL carries a specific receptor (CD20) in most if not all cases. This fact has led investigators to use a specific monoclonal antibody against the CD20 surface antigen, rituximab. Rituximab has been tried as a monotherapy and combined with chemotherapy, such as with CHOP, for the treatment of various types of lymphoma. R-CHOP is a well-known chemoimmunotherapy regimen that has been used for decades against adult B-cell lymphomas. It appears efficacious and well-tolerated. More recently, R-CHOP has been used for adult patients with NLPHL with promising results.

Recently, the Children Oncology Group (COG) evaluated three cycles of CHOP chemotherapy in 135 children with non-bulky stage IA and IIA NLPHL. The regimen was well tolerated, and only around 5% of patients had grade 3–4 fever and neutropenia. Eleven patients receiving CHOP had a less-than-CR and received involved-field radiotherapy. At a median follow-up of 62 months, the five-year estimated event-free survival (EFS) and overall survival (OS) rates were 89% and 100%, respectively.

There is a growing literature on the use of rituximab with chemotherapy in children with lymphoma. Such experiences will add more safety data supporting this approach.
R-CHOP for pediatric NLPHL

(chemoimmunotherapy). A randomised phase III trial has been published this year (2020) in the New England Journal of Medicine regarding the use of rituximab with chemotherapy for children with Burkitt lymphoma. This study adds more safety data regarding the use of rituximab with chemotherapy in children.9

Building on the results of the most recently published COG trial, which used CHOP as a chemotherapeutic backbone, and extrapolating from the long track record of adult experiences with R-CHOP, we decided to utilise R-CHOP to treat two children with NLPHL. R-CHOP appeared to be a tolerable regimen that achieved a CR in both cases. However, its long-term efficacy and safety data warrant further examination in children with NLPHL.

The accumulating long-term follow-up data for children treated with chemotherapy has alerted clinicians of serious long-term side effects that may take decades to appear.3 The current practice in paediatric oncology is to minimise long-term adverse events when possible. Targeted therapies, such as rituximab, are an example of such an approach. As has been successfully demonstrated in paediatric lymphomas, such as Burkitt lymphoma,9 we anticipate a similar path of combining rituximab with a chemotherapeutic backbone, such as CHOP, for children with NLPHL.

Conclusion

The combination of rituximab and CHOP is feasible and tolerable in children with low-risk NLPHL. Consistent with adult data, our data support the potential role of R-CHOP in children with NLPHL. Larger paediatric prospective trials are needed to address both the long-term efficacy and toxicity of such a regimen.

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Conflict of interest

The authors have no conflicts of interest to declare.

Ethical approval

Consent was provided by the primary caregivers for the purpose of publishing such cases. In addition, no identifying personal details are included in this manuscript.

Authors contributions

RF collected the historical and clinical and data and wrote the first draft. NA reviewed the data, conducted a literature review, and helped with manuscript writing. AA conceived and designed the study, reviewed the data, and edited the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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