

Clinical Utility of Radiological Disease Reassessment in the Management of Paediatric B-Cell Non-Hodgkin Lymphoma

Katherine Green¹, Vesna Pavasovic¹, Sara Ghorashian¹, Philip Ancliff¹, Jack Bartram¹, Anupama Rao¹, Sujith Samarasinghe¹, Ajay Vora¹, Danny Cheng^{1†}, David O'Connor^{1†}

¹*Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom.*

†DC and DOC contributed equally to this work

Correspondence Address:

Dr Katherine Green

Address: *Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK. WC1N 3JH.*

Email: katherine.green8@nhs.net

Phone: (+44) 02074059200

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Abbreviations Key:

Abbreviation	Full Phrase
BNHL	B-Cell Non-Hodgkin Lymphoma
BL	Burkitt Lymphoma
COP	COP chemotherapy (cyclophosphamide, vincristine, prednisolone)
CT	Computed Tomography
DLBCL	Diffuse Large B-Cell Lymphoma
FAB	French-American-British
FDG	Fluorodeoxyglucose
FDG-PET	Fluorodeoxyglucose- Positron Emission Tomography
LMB96	Lymphomes Malins B 96 study
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
PMLBL	Primary Mediastinal Large B-Cell Lymphoma
RA1	Radiological Assessment 1
RA2	Radiological Assessment 2
UK	United Kingdom
UKCCSG	United Kingdom Children's Cancer Study Group

Abstract

Although outcomes for children with B-Cell Non-Hodgkin Lymphoma (BNHL) are excellent, between 20-40% demonstrate residual radiological abnormalities at disease assessment during consolidation therapy. No studies have evaluated the significance of this. We report the outcomes for all children treated for BNHL at our centre over an 11 year period. Twenty-four of 64 (38%) children had residual radiological abnormalities at disease remission assessment. Seven (29%) underwent histological biopsies which were normal. No children with residual radiological abnormalities experienced disease relapse or death, suggesting that imaging at this timepoint creates clinical uncertainty without indicating residual disease or predicting relapse.

Introduction

Lymphomas are the third commonest malignancy in children¹ with most being high grade lymphomas such as Burkitt Lymphoma (BL) and Diffuse Large B-Cell Lymphoma (DLBCL). In general, children have excellent outcomes with survival rates of 85-92%²⁻⁴. Achieving complete response with induction chemotherapy is a key prognostic factor^{4,5}, as children with progressive disease or relapse, have dismal survival rates of less than 30%^{3,5-7}.

Given the importance of achieving complete remission, radiological assessments are performed at two time points to guide treatment escalation to those with residual or progressive disease (Supplementary Figure 1). Radiological Assessment 1 (RA1) occurs following pre-phase COP chemotherapy at day seven of treatment, where 'poor responders' can be escalated from Group B to C chemotherapy. Radiological Assessment 2 (RA2) occurs during consolidation to assess for residual disease which would require additional intensive chemotherapy.

Despite attempts to standardise disease response definitions, with the first International Paediatric Non-Hodgkin Lymphoma Response Criteria being published by Sandlund et al in 2015^{8,9}, residual radiological abnormalities at RA2 of uncertain significance are commonly found. Historically, 20-40% of children have radiological abnormalities identified during and at the end of treatment^{5,10,11}. However, even despite Sandlund's international response criteria, the clinical significance of residual abnormalities often remains uncertain without resection or biopsy to confidently exclude viable residual disease⁸. In this situation, clinicians face the difficult dilemma of whether to expose the child to an invasive biopsy or to perform serial radiological assessments to identify progressive disease. Both options carry a significant burden of uncertainty and expose the patient to an invasive procedure or additional radiation. Given that most children have an excellent outcome, the vast majority of these cases will not represent residual tumour, strongly questioning the value of disease assessment at the RA2 timepoint, as already demonstrated for end of treatment scans¹².

As it is well reported that survivors of paediatric BNHL have a significant risk of secondary malignancy^{2,13} minimising radiation exposure is an important consideration. To date, no studies have investigated the clinical utility of the RA2 timepoint for the early detection or prevention of disease relapse, with no consensus amongst UK treatment centres as to the optimal management of patients with residual radiological abnormalities. We therefore performed a retrospective analysis of all patients treated at our centre with BNHL over an 11 year period.

Methods

Patients

We undertook a retrospective analysis of all children diagnosed with high grade BNHL between 2006 and 2017 at Great Ormond Street Hospital. Data collected included demographics, histology, staging (Murphy's staging criteria), disease risk treatment group (using French-American-British Classification), treatment data, imaging modality at diagnosis and disease response assessment and patient outcome. All radiological assessments were performed by a consultant in paediatric radiology. Clinical judgment analysis determined whether additional reassessment imaging or biopsy altered clinical management or was deemed of clinical benefit to the patient in addition to the objective survival outcomes.

Treatment regimen

Patients were treated as per the UKCCSG FAB/LMB96 treatment protocol prior to 2010, and as per the Intergroup Inter-B-NHL-Ritux 2010 trial post-2010. Children treated between 2010-2015 were randomised to receive rituximab or not as per the study protocol randomisation, with all children treated since 2015 receiving rituximab as standard following removal of the randomisation. No alterations to clinical management were made by this study.

Results

Demographics

Sixty-five children aged 0-15 years were diagnosed with high-grade BNHL between 2006 and 2017. One child with BL was excluded as they had disease progression prior to the RA2 timepoint.

Mean age at diagnosis was 8.6 years (range 18 months - 15 years), with a male preponderance of 89% (57/64). Forty-seven of 64 (73%) patients had a histological diagnosis of BL, 16/64 (25%) DLBCL and 1/64 (2%) Primary Mediastinal Large B-Cell Lymphoma (PMLBL). Descriptive data of the patient cohort is presented in table 1.

Of the 64 children in this cohort, none were in treatment group A, 17 (27%) were group B, and 47 (73%) were group C, with 8 (12.5%) requiring escalation from group B to C following RA1 assessment. Twenty-four children (37%) were treated as per the FAB/LMB96 protocol, with the remaining 40 (63%) treated on the Intergroup Inter-B-NHL Ritux 2010 trial; all children diagnosed subsequent to 2015 received rituximab therapy as standard following closure of the trial randomisation. In total, 22 (34%) children received rituximab therapy, with no significant difference between presence of radiological residual abnormalities and rituximab therapy ($p < 0.05$)

Outcome

Three (4.7%) children died, two due to disease relapse on maintenance treatment (both following a good initial response to pre-phase chemotherapy with no residual radiological abnormalities at RA2), with failure of subsequent salvage chemotherapy, and one (patient 34) died due to secondary malignancy (Acute Myeloid Leukaemia) 4 years after treatment completion. Median follow-up duration was 99 months (8.25 years).

RA2 Disease Assessment

Twenty-four of 64 (38%) children had residual radiological abnormalities at RA2. The RA2 disease assessment imaging occurred at a median time of 83 days from diagnosis (range 65-111) in group B patients, and at 122 days from diagnosis (range 100-147) in group C patients. Imaging modalities used for disease re-assessment at RA2 included ultrasound in 26/64 children (41%), MRI in 23/64 (36%) and CT in 15/64 (23%).

Of the 24 children with residual abnormalities, seven (29%) underwent tissue biopsy for histological assessment (Table 2). In six children histology showed necrotic or fatty fibrous tissue, with inconclusive histology in the seventh case. Of the other 17 patients, 12 underwent additional follow-up imaging subsequent to RA2 to confirm complete remission (CR): a total of 20 additional ultrasounds, 5 CT scans and 7 MRI scans were performed. No children with residual abnormalities at RA2 received escalated chemotherapy and none suffered progressive disease or relapse. Of the 2 relapses seen in our cohort, neither had residual abnormalities at RA2.

Discussion

Our data confirm the excellent outcome of children with BNHL. Most importantly, however, our findings highlight the lack of clinical utility of the RA2 assessment, which frequently finds residual radiological abnormalities that are not related to disease.

The purpose of the RA2 imaging assessment is to identify residual disease to guide treatment intensification.. Our findings show that, despite the use of a contemporary regimen that includes rituximab, it remains common for children to have residual abnormalities at RA2. Furthermore, our data support the notion that the presence of residual abnormalities are unlikely to indicate viable tumour. No child with residual radiological abnormalities at RA2 relapsed or died (of lymphoma), whilst the two children in our cohort who did experience disease relapse had normal imaging at RA2 meaning relapse was not predicted by imaging at RA2. Similar results have been reported by Bhojwani et al¹¹ (2015) when assessing utility of FDG-PET/CT imaging for detection of viable residual tumour; where 18/73 (25%) patients with non-hodgkin lymphoma demonstrated residual radiological abnormalities on FDG-PET/CT or conventional

imaging modalities, with only 2/18 (11%) biopsies indicating viable tumour, and the remaining 89% representing necrotic, fibrotic, or inflammatory changes, despite 4/16 having concordant residual radiological abnormalities on both FDG-PET/CT and conventional imaging modalities.

Although unvalidated for paediatric BNHL, one limitation of our study is the lack of reassessment using fluorodeoxyglucose (FDG)-positron emission tomography (PET), which forms the mainstay of lymphoma assessment in adult protocols. Currently FDG-PET assessment is limited by its weak positive predictive value and low sensitivity for detection of early relapse⁴, although it has been shown to have a high negative predictive value in several small studies^{12,14}. This was confirmed by a recently presented Israeli study investigating the use of FDG-PET for early response assessment in 27 children which found residual masses in 25% of patients, all of which were negative on biopsy, suggesting little advantage over conventional imaging at this timepoint¹⁵. A further limitation of our study is the lack of radiological categorisation of residual abnormalities as per the International Paediatric Non-Hodgkin Lymphoma Response Criteria⁹.

Although small, our study suggests that the RA2 assessment timepoint is not a useful or reliable indicator of residual disease or future relapse. Instead, RA2 causes significant uncertainty and anxiety for approximately 40% of patients with BNHL with little clinical benefit in the detection or prevention of relapse. Larger collaborative studies, such as the ongoing French PET Lymphoma Study¹⁶, are now required to permit a standardised and balanced approach to the management of children with BNHL including consideration of removal of the RA2 assessment or a less risky and anxiety-inducing solution for the management of those with residual disease.

Conflict of Interest Statement

There are no conflicts of interest to declare.

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Table 1. Descriptive demographic and diagnostic data of patients with B-Cell Non-Hodgkin Lymphoma (BNHL) diagnosed between 2006-2017.

		<i>N=64</i>	Number of Children	Percentage (%)
		Demographic Data	Age at Diagnosis	0-4
5-9	34			54
10-14	20			31
15+	4			6
Gender	Male		57	89
	Female		7	11
Risk Factors	Bone Marrow (BM) Disease	BM Positive	13	20
		BM Negative	51	80
	Central Nervous System (CNS) Disease	CNS Positive	8	12
		CNS Negative	56	88
	MYC Status	MYC Positive	42	66
		MYC Negative	10	16
Unknown		12	18	
Histology	Diagnostic Histology	Primary Mediastinal Large B-Cell Lymphoma (PMLBL)	1	2
		Burkitt's Lymphoma (BL)	47	73
		Diffuse Large B-Cell Lymphoma (DLBCL)	16	25

Table 2. Summary of disease remission assessment abnormalities identified at Radiological Assessment 2

(RA2). DLBL = Diffuse Large B-Cell Lymphoma, MRI= Magnetic resonance imaging, CT = Computed Tomography.

Patient Number	Disease Classification	Disease Assessment Imaging Modality	Residual Abnormality Information	Histological Result if Biopsy performed	Imaging repeated for reassurance?	Outcome
12	Burkitt's	Ultrasound	Abdominal: Thickened small bowel and abnormal renal enhancement with no focal masses felt amenable to biopsy. Persistent ileocolic lymph nodes.	Biopsy not performed	Yes- 1 x Abdominal Ultrasound	Alive
13	Burkitt's	MRI	2 small renal lesions within 1cm diameter. Radiology report as likely fibrotic areas. To watch and wait as per protocol.	Biopsy not performed	Yes- 2 x Abdominal Ultrasounds	Alive
14	Burkitt's	Ultrasound / MRI	Enhancing liver lesion (segment 3) 2cm diameter felt unnameable to biopsy	Biopsy not performed	Nil	Alive
15	Burkitt's	MRI	Residual modularity in small bowel unamenable to biopsy.	Biopsy not performed	Yes- 2 x Abdominal Ultrasounds	Alive
17	Burkitt's	CT	Persistent Infra-temporal fossa mass and small residual in parapharyngeal space residual. Felt unnameable to biopsy. Other boney changes much improved	Biopsy not performed	Nil	Alive
18	DLBCL	MRI	Residual tumour extending intracranially through the left foramen ovale into the Meckel cave and the left cavernous sinus. Other boney changes much improved.	Biopsy not performed	Yes- MRI and CT head	Alive
21	Burkitt's	MRI	Right Orbit: massive reduction in lymphoma mass. Small mildly enhancing tissue superomedial to lacrimal gland.	Biopsy Performed: "inadequate sample". Biopsy not repeated as technically difficult.	Yes- 2 x MRI orbit	Alive
22	DLBCL	MRI	Left tonsillar mass with residual tissue on response status scan.	Biopsy Performed: "Tonsil benign, reactive lymphoid tissue only. No evidence lymphoma."	Nil	Alive
27	DLBCL	CT	Persistent Hilar lymphadenopathy and 1 ill-defined small right lung parenchymal nodule unnameable to biopsy	Biopsy not performed	Yes- 1 x MRI	Alive
28	Burkitt's	Ultrasound	Thyroid: persistent left abnormal heterogeneous thyroid lobe (right thyroidectomy) with surrounding lymphadenopathy.	Biopsy Performed: "Residual necrotic tissue, no lymphoma"	Yes- 1 x Ultrasound neck and 1 x MRI neck	Alive
30	DLBCL	CT → PET CT	Extensive chest/abdominal disease at presentation. At assessment 2 x 1.7cm residual mass between SVC and right atrial junction. Uterus appears abnormal. Much improved from presentation. Had negative PET CT.	Biopsy not performed	Nil	Alive
33	Burkitt's	MRI	Persistent nodule <1cm right kidney	Biopsy not performed	Yes- 3 x Abdominal Ultrasound	Alive
34	Burkitt's	Ultrasound and CT	3 x 3 cm mainly solid residual mass in the small bowel mesentery to the right of the IVC and inferior to the right lobe of the liver.	Biopsy Performed: "Necrotic tissue, no evidence lymphoma"	Yes- 4 x Abdominal Ultrasounds	Died (AML)
38	Burkitt's	MRI	Large para-pharyngeal tumour almost completely resolved. There is some asymmetry of the local soft tissues	Biopsy not performed	Nil	Alive
39	Burkitt's	CT	Small residual pelvic mass <2cm unnameable to biopsy	Biopsy not performed	Yes- 4 x Abdominal Ultrasounds	Alive
41	DLBCL	CT	Anterior mediastinal mass, almost fully resolved, persistent SVC occlusion. Unamenable to biopsy.	Biopsy not performed	Yes- 1 x CT	Alive
42	Burkitt's	CT	Small lesion related to the ramus of the right mandible with associated boney abnormality. Other existing disease resolved.	Biopsy not performed	Yes- 2 x CT	Alive
47	Burkitt's	Ultrasound	Small <6mm nodule in terminal ileum	Biopsy not performed	Nil	Alive
48	DLBCL	Ultrasound	Persistent subtle irregularity in the bony contour of the left body / angle of mandible without a defined residual mass to biopsy.	Biopsy not performed	Nil	Alive
49	Burkitt's	MRI	Abdominal mass with liver lesions at diagnosis. Residual abnormal intestinal mural thickening to the right in the pelvis. No focal lesion to biopsy.	Biopsy not performed	Yes- 1 x MRI and 3 x abdominal ultrasound	Alive
53	DLBCL	Ultrasound	Persistently enlarged and heterogenous lymph nodes at site of disease.	Biopsy not performed	Yes 1 x Ultrasound	Alive
100	Burkitt's	CT	Pulmonary lesions show necrotic low density changes, with persistent thickened lung parenchyma and bulky lymphoid subcarinal and hilar soft tissue.	Biopsy Performed: Reactive changes. No evidence of lymphoma.	Yes - 1 x CT	Alive
103	Burkitt's	MRI	Residual midline abdo-pelvis mass measuring 3 x 3.3cm demonstrating	Biopsy Performed: No active	Yes - 1 x USS abdomen	Alive

Supplementary Figure 1. A summary of the current chemotherapy schedule and scheduled radiological assessments 1 and 2 (RA1 and RA2) for children with B-Cell Non-Hodgkin Lymphoma (BNHL) treated as per the latest Intergroup Inter-B-NHL-Ritux 2010 trial.

