Improving outcomes of childhood and young adult non-Hodgkin lymphoma: 25 years of research and collaboration within the framework of the European Intergroup for Childhood Non-Hodgkin Lymphoma

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The European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL) was established 25 years ago with the goal to facilitate clinical trials and research collaborations in the field both within Europe and worldwide. Since its inception, much progress has been made whereby major improvements in outcomes have been achieved. In this Review, we describe the different diagnostic entities of non-Hodgkin lymphoma in children and young adults describing key features of each entity and outlining clinical achievements made in the context of the EICNHL framework. Furthermore, we provide an overview of advances in biopathology with an emphasis on the role of biological studies and how they have shaped available treatments. Finally, for each entity, we describe future goals, upcoming clinical trials, and highlight areas of research that require our focus going forward.

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Introduction

Like other collaborations, the European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL) began when colleagues were discussing a problem common to many paediatric malignancies, that of small patient numbers necessitating international collaboration to answer clinical questions and improve treatment outcomes.

Initial discussions took place at the International Conference on Malignant Lymphoma in Lugano, Switzerland, in June 1993 and focused on the diagnosis and optimal management of anaplastic large cell lymphoma, a rare malignancy accounting for 10–15% of childhood non-Hodgkin lymphoma, with no consensus regarding a standard treatment approach. Subsequently, the first EICNHL meeting, consisting of a group of clinicians, pathologists, and statisticians, took place in Padua, Italy, in 1995. Several national groups were represented including Société Française d'Oncologie Pédiatrique, the UK Childhood Cancer Study Group, Berlin-Frankfurt-Munster (NHL-BFM), Associazione Italiana di Ematologia e Oncologia (AIEOP), Nordic Paediatric Haematology and Oncology association (NOPHO), and the Dutch Childhood Leukaemia and Lymphoma Study Group. Stratification for the first anaplastic large cell lymphoma clinical trial run by the collaborative group, ALCL99, was based on an analysis of risk factors that used a combined dataset from national trials.

In the eary to mid-1990s, the importance of pathology in terms of diagnostic, morphological, and molecular criteria was recognised, and pathology review panels were convened to review atypical cases of anaplastic large cell lymphoma. The additional involvement of scientists bringing with them an understanding of the biology of anaplastic large cell lymphoma, particularly the immune response in patients with anaplastic large cell lymphoma, and the ability to molecularly monitor early stages of disease led to the development of a multidisciplinary team working together under the umbrella of EICNHL. With the roll out of the anaplastic large cell lymphoma study, membership was widened to include Poland, Hungary, Japan, and Spain, with not only more clinicians, but also pathologists, scientists, and statisticians joining the group. This increase in size and complexity necessitated the development of guidelines to underpin successful collaboration.

Since these early days, the group has considerably increased in the number of members, not just in terms of countries (eg, a closer working relationship with colleagues in the USA and with the international Berlin-Frankfurt-Munster (i-BFM) group has been established), but also individuals with diverse interests. The group now has a clinical chair and a basic research chair to ensure meaningful engagement of both communities in the problems faced. Frontline and relapse strategy optimisation for the major non-Hodgkin lymphoma subtypes, and diagnostic and therapeutic consensus for rarer lymphomas, based on retrospective multinational analyses, have been pursued. Importantly, engagement of EICNHL with early clinical trial groups and pharmaceutical companies enables studies with new drugs to be done for children with first-line or relapse disease. The EICNHL thrived on the clinical and scientific

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needs to collaborate on rare conditions in children, but collaboration has been cemented by social interactions and the hospitality of national groups.

The incidence and range of childhood non-Hodgkin lymphomas

Non-Hodgkin lymphoma is a heterogeneous group of lymphoid malignancies that accounts for 7% of cancers diagnosed in people younger than 20 years residing in high-income countries (table 1). The incidence increases steadily throughout life (from 5·9 per million in children <5 years old, to 150 per million in adults 20 or more years old), and varies by geographical region, pathology, and sex. More than 90% of children present with high-grade Non-Hodgkin lymphoma.[1]

The aetiopathogenesis of childhood non-Hodgkin lymphoma

The aetiopathogenesis of childhood non-Hodgkin lymphoma is poorly understood, although environmental exposures might have a role in some. For example, birth in the spring or summer compared with autumn and winter has been associated with an increased risk of non-Hodgkin lymphoma in a population-based cohort study in Sweden, possibly related to delayed infectious exposures.[2] Although Epstein-Barr virus (EBV) infection is well-recognised to be closely associated with endemic Burkitt lymphoma in sub-Saharan Africa,[3] EBV-seropositivity is also common in children diagnosed with Burkitt lymphoma in central Europe, supporting the theory that EBV exposure increases the risk of sporadic childhood Burkitt lymphoma.[4] Other, yet unknown, infectious exposures might also be involved in at least some childhood and young adult non-Hodgkin lymphomas (children and young adults; includes patients ranging in age from birth to 39 years, although age limits vary between clinical studies).[5] Moreover, children with acquired or inherited immunodeficiency and those with DNA-repair disorders or constitutional mismatch repair deficiencies, are predisposed to non-Hodgkin lymphomas.[6]

	Cellular origin	Incidence (%)
Mature B-cell lymphomas		
Burkitt lymphoma or leukaemia	B cell	35–40%
Diffuse large B-cell lymphoma	B cell	10–15%
Other (eg, primary mediastinal B-cell lymphoma, follicular lymphoma, or marginal zone lymphoma)	B cell	5–10%
Lymphoblastic lymphoma	B cell or T cell	20–25%
Anaplastic large cell lymphoma	T cell	10–15%
Rare T-cell lymphomas, eg, peripheral T-cell lymphoma not otherwise specified, extranodal NK or T-cell lymphoma, hepatosplenic T-cell lymphoma, and subcutaneous panniculitis-like T-cell lymphoma	T cell	10%

Table 1: **Major diagnostic subtypes, cellular origins, and incidences of childhood and young adult non-Hodgkin lymphomas (% of all cases)**

However, some non-Hodgkin lymphomas in children and young adults are associated with distinct genetic events such as the t(2;5)(9p23;q35) generating the NPM-ALK fusion in anaplastic large cell lymphoma and the t(8;14)(q24;q32) involving *MYC* and immunoglobulin heavy-chain locus in Burkitt lymphoma.[7,8] Both events are considered to be the driving genetic events of these malignancies, although why they occur and the cell type in which they are generated remains to be fully determined. What is clear is that their presence alone is insufficient for lymphomagenesis. For example, in the case of NPM-ALK driven anaplastic large cell lymphoma, it has been proposed that early thymic progenitors are the source of the translocation that is propagated through subsequent T-cell development generating primed peripheral T cells, which, following a second oncogenic stimulus, perhaps a consequence of some infectious exposure, transform into a malignancy.[5,9] Regardless of the mechanism, these translocation products provide valuable biomarkers.

Diagnosis and staging

Risk-adapted treatment strategies rely on correct diagnosis and staging. The revised International Paediatric non-Hodgkin lymphoma Staging System improves on the St Jude classification by incorporating knowledge of newly characterised paediatric non-Hodgkin lymphomas, specifying the meaning of some disease sites, and collecting data gained with sensitive methods such as immunophenotyping, molecular genetics (used to detect minimal disseminated disease [MDD] or minimal residual disease [MRD]), and imaging technologies.[10,11] The role of [^{18}F]flurodeoxyglucose ([^{18}F]FDG)-PET-CT in childhood non-Hogdkin lymphomas has yet to be established. A French prospective trial showed the very limited effect of [^{18}F]FDG-PET-CT on initial staging compared with conventional imaging and suggested that this method might be misleading regarding bone marrow involvement.[12] The International Paediatric non-Hodgkin Lymphoma Response Criteria defines response to treatment in childhood NHL and incorporates both contemporary diagnostic imaging (PET-CT and MRI) and pathological analysis.[13] This work involving members of EICNHL, St Jude Children's Research Hospital, and the Children's Oncology Group (COG) will be incorporated into ongoing trials as the general paediatirc oncology community aims to better assess the prognostic effect of metabolic response in paediatric non-Hodgkin lymphomas and to harmonise staging and response, allowing comparisons between study groups, reproducibility of staging, and response assessments.

The design of clinical trials and drug development for non-Hodgkin lymphomas in children, adolescents, and young adults

There are still no special methods for designing, carrying out, or analysing clinical trials in small populations as

	Type of study	Phase	Inclusion criteria	Backbone	Random-isation	Experimental drug or strategy	Participants, N	Event-free survival*	Overall survival *
Inter-B-NHL Ritux 2010	Clinical trial[17]	3	HR-B-NHL; <18 years	FAB LMB 96-based block therapy alone or combined with rituximab	Yes	Rituximab	328	93·9% (95% CI 89·1–96·7) with randomisation plus chemotherapy *vs* 82·3% (75·7–87·5) with chemotherapy alone at 3 years	95·1% (95% CI 90·5–97·5) with randomisation plus chemotherapy *vs* 87·3% (81·2–91·6) with chemotherapy alone at 3 years
Inter-B-NHL Ritux 2010	Clinical trial[19]	2	PMLBL; <18 years	DA-EPOCH-R	No	Rituximab	46	69·6% at 4 years (95% CI 55·2–80·9)	84·8% at 4 years (95% CI 71·8–92·4)
B-NHL BFM 2004	Observational study (final report , unpublished)	NA	All B-NHL grades; ≤18 years (no PMLBL)	NHL-BFM-based block therapy	No	Standard of care	863	88% at 2 years	92% at 2 years
LMB01-PMLBL stratum	Observational study[20]	NA	PMLBL; ≤18 years	FAB LMB 96-based block therapy combined with rituximab	No	Rituximab	21	95·2% (95% CI 77·3–99·2) at 5 years	100% at 5 years
EURO-LB-02	Clinical trial[21]	3	LBL; <22 years	ALL-based therapy	Yes	Dexamethasone (T-LBL); reduction of maintenance phase (T-LBL); no prophylactic CNS radiotherapy; these questions could not be answered due to premature closure of the trial due to a 3·8% toxic death rate	319 total; 233 for TLBL; 66 for BCP-LBL	82% (95% CI 78 to 86) overall at 5 years; 82% for T-LBL; 80% for BCP-LBL	87% (95% CI 91 to 99) overall at 5 years
ALCL99	Clinical trial[20–24]	3	ALCL; ≤21 years	B-NHL BFM-based therapy	Yes	All registered patients	420	10-year progression-free survival: 70% (95% CI 64–76)	10-year overall survival: 90% (95% CI 88–92)
ALCL99 R1	Clinical trial[22–23]	3	ALCL; ≤21 years	B-NHL BFM-based therapy	Yes	HD methotrexate 3 g/m² per 3 h *vs* 1g/m² per 24 h and intrathecal therapy	352	73·7% in methotrexate 1 group; 74·5% methotrexate 3 group at 2 years (HR 0·98; 92% CI 0·69–1·38)	90·1% in methotrexate group 1; 94·9% in methotrexate 3 group at 2 years (HR 0·67; 92% CI 0·36–1·25)
ALCL99 R2	Clinical trial[20–23]	3	High-risk ALCL defined by involvement of the mediastinum, viscera, skin, or all	B-NHL BFM-based therapy	Yes	Standard chemotherapy *vs* standard chemotherapy and vinblastine during induction and at maintenance for a total duration of treatment of 1 year	110	72·5% (for groups also receiveing VBL) *vs* 70·1% at 2 years (95% CI 0·55 to 1·5)	94% at 2 years with no difference between groups (95% CI 0·49–3·38)
NA	Retrospective[24]	NA	PTFL	Any	No	Any	63	94% at 2 years	100% at 2 years
NA	Retrospective[24]	NA	pMZL	Any	No	Any	66	70% at 5 years	98% at 5 years
NA	Retrospective[24]	NA	Non-anaplastic PTCL	Any	No	Any	143	45% at 5 years	56% at 5 years

(Table 2 continues on next page)

stated in the European Medicines Agency guidelines.[14] One of the design options for trials in rare diseases, which has been discussed within the international rare cancers initiative, is interventional in nature and usually randomised with an increased α error of 10% compared with the normally used 5%.[15] In addition, trials that not only have clinical endpoints, but also facilitate biological studies involving multiple countries, make it possible to prospectively validate the results of previous research. Deeper knowledge of the biology of the main subtypes of non-Hodgkin lymphomas in children and young adults has promoted a shift towards a personalised medicine approach based on biomarker-driven risk stratification strategies and evaluation of new targeted therapies within international clinical trials.

Mature B-cell non-Hodgkin lymphomas

Clinical achievements

Cures for children and adolescents with high-grade, mature B-cell non-Hodgkin lymphoma (mainly Burkitt lymphoma but also diffuse large B-cell lymphoma) have greatly improved in the past four decades with overall survival rates of about 75% in the 1980's improving considerably to about 95% in more recent studies conducted in the 2000s.[16–18] For high-risk disease (stage 3 with elevated lactate dehydrogenase, stage 4, or leukaemia, or both), a 2011, joint

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	Type of study	Phase	Inclusion criteria	Backbone	Random-isation	Experimental drug or strategy	Participants, N	Event-free survival*	Overall survival*
(Continued from previous page)									
R-VICI	Observational study[25]	NA	Relapsed-refractory B-cell lymphoma, most patients not previously exposed to rituximab	Continuous infusion chemotherapy and allogeneic HSCT	No	vincristine, ifosfamide, carboplatin, and idarubicin-block, and rituximab	15	Not known	67% at 4 years (95% CI 43–91)
Re-induction of remission	Retrospective[26]	NA	Relapsed–refractory T-cell lymphoblastic lymphoma	HR-ALL-like treatment regimens and allogeneic HSCT	No	high-risk-blocks	177	Not known	27% at 8 years (95% CI 21–33)
ALCL relapse trial 2004	Clinical trial[27]	3	Relapsed–refractory anaplastic large cell lymphoma; ≤21 years	Risk-adapted strategy: stratification according to time of relapse or progression and CD3 status	No	All eligible patients	105	53% at 5 years (95% CI 43–62)	78% at 5 years (95% CI 69–85)
As above	As above	As above	As above	As above	As above	Very early relapse: allogeneic SCT after reinduction chemotherapy	17	41%† at 5 years (95% CI 23–73)	59% at 5 years (95% CI 40–88)
As above	As above	As above	As above	As above	As above	CD3-positive relapse: allogeneic SCT after reinduction chemotherapy (autologous if no 10/10 donor)	26	62%† at 5 years (95% CI 45–83)	73% at 5 years (95% CI 58–92)
As above	As above	As above	As above	As above	As above	Relapse within 1 year and CD3 negative: autologous SCT (BEAM) after reinduction chemotherapy‡	32	44%† at 5 years (95% CI 29–65)	78% at 5 years (95% CI 65–94)
As above	As above	As above	As above	As above	As above	Late relapse, CD3 negative: vinblastine given once per week for 24 months	21	81%† at 5 years (95% CI 66–100)	90% at 5 years (95% CI 79–100)

B-NHL=B-cell non-Hodgkin lymphoma. FAB LMB=French American British Lymphoma malins B. HR=high risk. PMLBL=primary mediastinal large B cell lymphoma. DA-EPOCH-R=dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab. NA=not applicable. NHL=non-Hodgkin lymphoma. BFM=Berlin-Frankfurt-Munster. LBL=lymphoblastic lymphoma. ALL=acute lymphocytic lymphoma. T-LBL=T lymphoblastic lymphoma. ALCL=anaplastic large cell lymphoma. HD=high dose. VBL=vinblastine. PTFL=primary t follicular lymphoma. pMZL=primary marginal zone lymphoma. BL=Burkitt lymphoma. HSCT=haematopoietic stem-cell transplantation. BEAM=carmustine, etoposide, cytarabine, and melphalan. *95% CI are given when reported in the respective publications. †Event-free survival and overall survival rates according to intention to treat. ‡Patients with a CD3-negative relapse within 1 year after initial diagnosis or before exposure to vinblastine (intermediate risk) received autologous HSCT after carmustine-etoposide-cytarabine-melphalan. This group was terminated prematurely, and subsequent patients received vinblastine monotherapy instead.

Table 2: **Outcomes from past and ongoing front-line therapy clinical trials within the European Intergroup for Childhood Non-Hodgkin Lymphoma framework**

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EICNHL and COG randomised phase 3 trial (NCT01516580), showed that the addition of six doses of rituximab to the lymphoma malins B (LMB) chemotherapy backbone (vincristine, cyclophosphamide, methotrexate, doxorubicin, cytarabine, cytarabine arabinoside, etoposide, and prednisolone) improved event-free and overall survival but was associated with an increase in myelotoxicity and hypogammaglobulinemia (table 2). However, the use of rituximab for children with standard-risk disease (about 40% of patients) has not reached a consensus, as survival for these children following treatment with BFM chemotherapy (prednisolone, vincristine, cyclophosphamide, cytarabine, doxorubicin, methotrexate, ifosfamide, etoposide, dexamethsone, vindesine) or LMB chemotherapy is already very high (97–98%) and although these protocols are associated with acute toxicity, fatal events are rare and long-term sequelae are limited.[28]

A phase 2 international EICNHL and COG trial (NCT01516567) for primary mediastinal large B-cell lymphoma of 46 patients in which rituximab was given in combination with dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R), did not show any improvement in survival with a long-term event-free survival of 70% (95% CI 55·2–80·9) and overall survival of 85% (95% CI 71·8–92·4). The results were similar to historical controls with paediatric chemotherapy-only regimens (table 2).[19] This outcome is in contrast with the BFM series reporting an event-free survival of 84% (95% CI 72–91) after DA-EPOCH-R treatment.[19,29] Moreover, the observation of isolated and combined CNS relapse cases in the EICNHL and COG trial (NCT01516567) and NHL-BFM prospective registry raises concerns, as these were very rarely reported in historical paediatric series.[30] Thus, further prospective trials are required for primary mediastinal large B-cell lymphoma to test alternative regimens including CNS prophylaxis or novel agents (eg, NF-KB pathway inhibitors or anti-PD1 therapies).

Identification of different diagnostic entities of B-cell non-Hodgkin lymphomas

Three major areas of progress have been made in the last two decades concerning the diagnosis and definition of B-cell non-Hodgkin lymphomas, specifically in children and young adults. Applying gene expression profiling and genomic analysis, the homogeneity of Burkitt lymphoma and its genetic distinction from diffuse large B-cell lymphoma has been clearly established.[31,32] However, Burkitt lymphoma in children and young adults, unlike in adults for whom Burkitt lymphoma and diffuse large B-cell lymphoma have overlapping features, can be reliably diagnosed by morphology, immunohistochemistry, and fluorescence in-situ hybridisation alone.[33] Similarly, primary mediastinal large B-cell lymphoma has been shown to be clinically and molecularly distinct from diffuse large B-cell lymphoma.[34] Moreover, diffuse large B-cell lymphoma in the childhood and young adult population is largely a mature B-cell lymphoma of a germinal-centre-like B-cell (GCB) subtype[35,36] in contrast to adults among whom approximately 50% of cases have an activated B-cell origin with a continuous decline in the frequency of the GCB subtype with age.[37] Diffuse large B-cell lymphoma diagnosed in adults, was further subcategorised in 2018, with a multiomics approach including whole-exome sequencing, RNA sequencing, and copy number analysis describing as many as seven different genetic subtypes with different survival outcomes.[38,39] However, so far, how paediatric diffuse large B-cell lymphoma fits into this new subclassification system remains uncertain.

In parallel, newly defined morphological and genetic subtypes of mature, aggressive, B-cell lymphomas have been described in children and young adult patients, including high-grade B-cell lymphoma with 11q aberration (HGBCL-11q) and large B-cell lymphoma with *IRF4* translocation (LBCL-IRF4). These have subsequently been introduced into the 2022 WHO classification of haematopoietic and lymphoid malignancies and the International Consensus Classification of Mature Lymphoid Neoplasms (although HGBCL-11q is called HG/large(L)BCL-11q).[40,41] These newly described subtypes are far rarer in adults and have clinically distinct genetic features that differentiate them from conventional Burkitt lymphoma and diffuse large B-cell lymphoma. Future challenges will be to establish whether affected patients will benefit from different therapeutic protocols to the currently used ones for the treatment of children and young adults with Burkitt lymphoma and large B-cell lymphoma.

Advances in understanding of the biology of mature B-cell non-Hodgkin lymphomas: towards improving patient outcomes

Research done in the last two decades has given rise to improved molecular techniques that have facilitated progress, including PCR to detect low amounts of *MYC*-IgH fusion sequences or immunoglobulin IG-rearrangements in the peripheral blood or bone marrow of patients, allowing assessment of MDD and MRD (table 3). In this manner, retrospective studies of patients with Burkitt lymphoma and leukaemia treated within the national AIEOP LNH-97 protocol showed negative prognostic value of MDD at diagnosis, and MRD following the first course of chemotherapy.[42,43,51] Furthermore, MRD analysis early in the disease course might also be an essential tool for monitoring treatment response in the setting of chemoimmunotherapies as was shown for the NHL-AIEOP trial. Thus, MDD and MRD analysis was implemented in the Inter B-NHL ritux 2010 (NCT01516580) and B-NHL 2013 (NCT03206671) trials.

Sequencing technologies have allowed an in-depth study of the genetics underlying childhood and young adult mature B-cell non-Hodgkin lymphoma and subsequently an improved understanding of the biology of these

	Method of detection	Clinical significance*
B-cell non-Hodgkin lymphoma		
Myc-IgH fusion; t(8;14) translocation[42]	LD-PCR	Correlation with PFS; MDD and early MRD for advanced disease; needs prospective validation
Immunoglobulin-rearrangements[43]	PCR	Correlation with PFS; MDD and early MRD for advanced disease; needs prospective validation
TP53[44,45]	NGS	Correlation with PFS; needs prospective validation
Lymphoblastic lymphoma		
Notch1mut, FBXW7mut, or both[46,47]	NGS	55% (29/53), good prognosis (improved 5-year EFS of 96% *vs* 45% [95% CI 0·01–0·7] and overall survival of 96% *vs* 59%)
KMT2Dmut, PTENmut, or both[47]	NGS	22% (27/123), poor risk if *Notch1/FBXW7* wild-type (11/27; 11% *vs* 37% relapse incidence at 5 years; 95% CI 1·1–170·5)
Anaplastic large cell lymphoma		
Small cell/ lymphohistiocytic (SC/LH) variant[24]	Histopathology	29% (121/420) SC/LH component; high relapse risk (HR 2·49; 95% CI 1·71–3·63) but interobserver variation
Anti-ALK autoantibodies[48]	Immunoassay	Low antibody titre (titre ≤1/750): 30% (39/128); high relapse risk (HR 3·8; 95% CI 2·0–7·1) but a standardised assay is required
ALK MDD or MRD[23,48]	RT-PCR	Quality control established; about 20% (40–50% of patients who are MDD positive with available MRD) MRD-positive before the second course (very high risk), EFS 19% (95% CI 3–35); MDD and MRD used for stratification
ALK MDD or MRD[48]	qRT-PCR	20% (18/91) high MDD with high to very high-risk (EFS 33%; 95% CI 11–55), interlaboratory comparison not possible
ALK MDD or MRD[49]	ddPCR	32% (67/204) high MDD with relapse risk (EFS 34%; 95% CI 24–44) interlaboratory quality control possible
Exosomal cargo (specifically, microRNAs)[50]	RT-PCR	Correlation with tumour dissemination and prognosis; requires prospective validation

NGS=next generation sequencing. ddPCR=digital droplet PCR. RT-PCR=reverse transcriptase PCR. qRT-PCR=quantitative reverse transcriptase PCR. MDD=minimal disseminated disease. MRD=minimal residual disease. Ig=immunoglobulin. PFS=progression free survival. EFS=event free survival. IgH=immunoglobulin heavy chain. *95% CIs are given when reported.

Table 3: **Current status of biomarkers for prognostication and disease monitoring of children and young adults with non-Hodgkin lymphomas**

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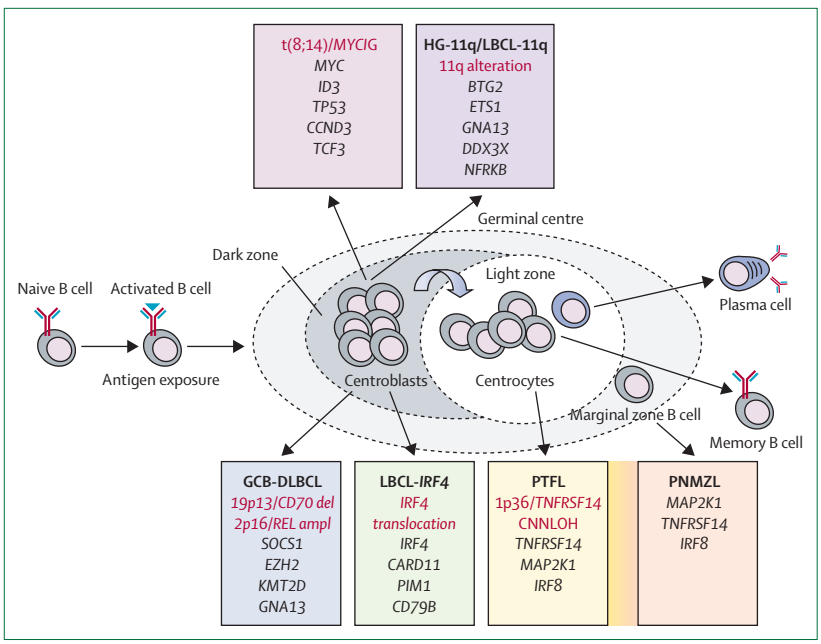

Figure: **Molecular landscape of paediatric aggressive B-cell non-Hodgkin lymphomas**
Schematic representation of the different entities of paediatric aggressive B-cell non-Hodgkin lymphomas according to their normal cellular counterparts determined by their similarity in immunophenotype, histological appearance, and gene expression profiles. Structural variants are indicated in red and key mutated genes associated with the different entities are listed below. Subtypes with overlapping features are shown as a colour gradient. HG=high grade. LBCL=large B-cell lymphoma. GCB-DLBCL=germinal centre B-diffuse large cell lymphoma. PTFL=Primary T-cell follicular lymphoma. PNMZL=Primary nodal marginal zone lymphoma.

malignancies (figure). Mutations in at least one of the three genes involved in the *ID3–TCF3–CCND3* pathway have been identified in over 88% of cases of *MYC*-rearranged B-cell non-Hodgkin lymphoma, suggesting these mutations might represent a crucial second hit in the pathogenesis of childhood Burkitt lymphoma resulting in increased B-cell receptor signalling and cell proliferation.[44,52,53] Globally, diffuse large B-cell lymphoma in children are predominantly of a GCB subtype and carry recurrent mutations of *SOCS1* and *KMT2D*, gains of *2p16/REL* and losses of *19p13/CD70*,[54] but virtually lack *MYD88* (Leu265Pro), *NOTCH1, NOTCH2, BCL2,* and *SGK1* mutations that have previously been associated with established mutational clusters in adult large B-cell lymphoma. In addition, *TP53* mutations, a high level of genetic complexity and an activated B cell of origin are associated with a poor prognosis in childhood and young adult diffuse large B-cell lymphoma. Moreover, patients who relapse can be characterised by *TP53* inactivating mutations suggesting that drugs targeting the degradation of mutant p53 or restoration of wild-type p53 might represent novel therapeutic approaches.[45,55]

Regarding the molecular features of newly identified subtypes such as HG/LBCL-11q and LBCL-IRF4, the HG/LBCL-11q lack Burkitt lymphoma-specific gene mutations (*ID3*, *TCF3*, and *CCND3*) but have recurrent mutations of *BTG2, DDX3X, EP300, ETS1,* and *GNA13*. Therefore, at the molecular level, the tumour appears to be more closely related to large B-cell lymphoma rather than Burkitt lymphoma as initially suggested. By contrast, LBCL-IRF4 carry frequent mutations of *IRF4* and NF-κB pathway genes (*CARD11, CD79B,* and *MYD88*) suggesting a key role for deregulation of this pathway in the pathogenesis of this group of tumours. Finally, a novel resource of paediatric Burkitt lymphoma patient-derived xenografts,[56] in combination with all other molecular approaches established within EICNHL, will allow us to better elucidate mechanisms of resistance and to improve the situation for the worse prognosis patient population in the future.

The future of mature B-cell non-Hodgkin lymphoma treatment for children and young adult patients and treatment of resistant disease

The NHL-BFM and NOPHO trial B-NHL 2013 (NCT03206671) are recruiting patients with low, standard, and high-risk B-cell non-Hodgkin lymphomas. Patients are treated with a rituximab window before standard NHL-BFM chemotherapy, evaluating one versus seven doses of rituximab in advanced stage paediatric B-cell non-Hodgkin lymphoma (table 4). Future strategies for children and young adults with B-cell non-Hodgkin lymphoma will probably incorporate rituximab for all risk groups to allow for a major reduction of cytotoxic chemotherapy and toxicity. However, given the very poor outcome of patients with refractory or relapse disease, doing such a study is challenging and will require the development of additional biomarkers to better stratify therapy and evaluate disease response.

Relapses of children and young adults with B-cell non-Hodgkin lymphoma are rare, but their outcome is very poor, especially for patients with Burkitt lymphoma exposed to rituximab in the frontline setting.[17,25] As there are many medicines being developed for B-cell non-Hodgkin lymphoma in adults, but few for children, a Paediatric Strategy Forum (convened by the multi-stakeholder organisation, ACCELERATE, and the European Medicines Agency), was held to discuss drug development specifically for children.[57] At this point in time, CAR T cells, T-cell engagers, and antibody drug conjugates have been identified as having the greatest probability of providing benefits for relapsed patients. For this purpose, a global overarching study of novel agents in relapsed or refractory B-cell non-Hodgkin lymphoma (Glo-BNHL) was launched in 2022 as an academic-led, industry partnership to generate data fit for regulatory filing. Glo-BNHL is an international multicohort platform trial that will make the parallel assessment of only the most promising agents feasible, prioritised upfront by an independent Trial Steering Committee following predefined criteria. Clear stopping rules will allow agents to be replaced efficiently exposing the smallest number of children possible to any ineffective therapy. The inclusion of three treatment groups enables patient entry into the study at different stages of treatment and disease

	Phase	Inclusion criteria	Planned recruitment (year and number of patients)	Strategy	Randomisation	Biomarker driven	Experimental drug or strategy	Trial number
Mature B-NHL								
B-NHL 2013 (NHL-BFM-NOPHO)	3	Aggressive mature B-NHL; <18 years	2017–22; N=650	NHL-BFM-based block therapy	Yes	No	B-NHL BFM 04 with rituximab window replacing anthracyclines in patients at low risk, with randomised rituximab window in patients at intermediate risk, and rituximab window and randomised 6 additional doses for patients with HR	NCT03206671
Glo-BNHL	2	Any B-NHL histology, any previous treatment; ≥6 months and <25 years	2023–29; N=210	Multiarm targeted therapy strategy	No	No	Arm 1: BiTE; arm 2: ADC in combination with RICE; arm 3: CAR T	EudraCT 2021-004283-10
LBL								
LBL 2018	3	LBL; <18 years	2019–24; N=650	EURO-LB-02	Yes	T-LBL: *NOTCH*/*FBXW* 7 mutational status	Prednisone *vs* dexamethasone in induction; Intensified *vs* standard treatment in HR	NCT04043494
HEM-iSMART	1/2	LBL in first or greater relapse or refractory to at least one previous induction regimen; <18 years	2023–26; N=60	Multiarm targeted therapy strategy	No	Molecular stratification	Master protocol trial with substudies according to the molecular profile of the disease	EudraCT 2021-003398-79
ALCL								
ALCL-VBL	3	ALK + ALCL; <18 years; only patients who are MDD negative	2021–26; N=106	Chemotherapy, single agent	No	MDD (ALK-fusion transcripts)	Vinblastine	EudraCT 2017-002935-40
BrigaPed	1/2	ALK + ALCL; refractory disease (ie, MRD positive after 1 course of chemotherapy) or any relapse; 1 year to 25 years	2022–30; N=65	Targeted therapy, single agent	No	No	Brigatinib	NCT04925609
CRISP	1/2	ALK + ALCL; Any previous treatment; 1–21 years	2009–27; N=6 (ALCL arm 1B)	Targeted therapy, single agent	No	No	Crizotinib	NCT00939770
Nivo-ALCL	2	ALK + ALCL; >6 months of age	2019–28; N=38	Targeted therapy, single agent	No	No	Nivolumab; cohort 1: any previous treatment with ALK inhibitor, or brentuximab–vedotin, or both for patients with progressive disease; cohort 2: as consolidative immunotherapy instead of allogeneic SCT for patients in complete remission	NCT03703050

B-NHL=B cell non-Hodgkin lymphoma. LBL=lymphoblastic lymphoma. ALCL=anaplastic large cell lymphoma. HR=high risk. CAR T=chimeric antigen receptor T cell. SCT=stem cell transplant. BiTE=bispecific T cell engager. ADC=antibody drug conjugate. RICE=rituximab, ifosfamide, carboplatin, and etoposide. MDD=minimal disseminated disease.

Table 4: **Ongoing front-line therapy clinical trials within the European Intergroup for Childhood Non-Hodgkin Lymphoma framework**

progression, to allow access to the most promising new drugs for each patient with resistant disease.

Lymphoblastic lymphoma

Clinical achievements and biological insights towards improved patient management

EICNHL together with international co-operative partners led the EURO-LB-02 clinical trial (2007-005396-34), which resulted in event-free and overall survival probabilities exceeding 80%.[21] Despite progress with frontline treatment, therapy for patients with refractory or relapsed lymphoblastic lymphoma remains challenging.

Ongoing research efforts aim to improve event-free survival by identifying patients with high-risk disease in need of intensive treatment, and to avoid unnecessary exposure of patients at low risk to toxicity. A 2012, retrospective analysis of T-cell lymphoblastic lymphoma identified *NOTCH1* and *FBXW7* mutations as favourable biomarkers in five independent studies, LOH6q and $PTEN^{mut}$ as indicators of a worse outcome in the NHL-BFM patient cohort studies, and an absence of biallelic T-cell receptor deletions as an unfavourable prognostic marker in the French patient series (table 3).[52,58] Meta-analysis of the Italian (AIEOP; n=73), French (SFCE; n=80), and the German (NHL-BFM; n=114) T-cell lymphoblastic lymphoma series confirmed the prognostic relevance of the mutational status of *NOTCH1* and *FBXW7* (unpublished data) which now serve as risk stratification criteria in the international lymphocytic lymphoma 2018 trial (2017-001691-39). Furthermore, in 2021, genome-wide studies have identified *KMT2D* as a biomarker for poor prognosis and *mir223* overexpression as a potential poor

prognostic marker for T-cell lymphoblastic lymphoma, which need to be validated in prospective trials (table 3).[47,58] In addition, efforts have been made to adapt MDD and MRD evaluation for T-cell lymphocytic lymphoma; initial analyses associated a poor prognosis with MDD positivity,[58] but this association has not been confirmed in the 2021, COG[59] and EURO-LB-02 studies,[60] perhaps reflective of different therapeutic approaches.

Advances in improving the diagnosis of lymphoblastic lymphoma

Differential diagnosis of lymphoblastic lymphoma as compared with mature lymphomas is usually determined by morphology, followed by immunophenotyping with numerous antibodies directed against both B cell and T cell as well as myeloid antigens; guidelines for characterisation by multicolour flow cytometry are essentially those of acute lymphoblastic leukaemia.[61,62] Since lineage determination on formalin-fixed paraffin-embedded tissue can be challenging for minimally differentiated tumours lacking specific markers, bilineage or multilineage marker expression, or tumours lacking immature antigens, EICNHL developed an algorithm for tissue-based immunophenotyping of lymphoblastic lymphoma in which terminal deoxynucleotidyl transferase (TdT) expression was identified as the best marker for determining the precursor origin of this group of malignancies.[63] In rare cases of TdT negative lymphoblastic lymphoma, expression of CD1a or CD34, coexpression of CD79a and CD3, or CD4 and CD8 can be used to confirm the precursor cell nature of these lymphomas. In contrast to acute lymphoblastic leukaemia, immunophenotypical and molecular studies using tissue biopsies of lymphoblastic lymphoma are rare and are mostly restricted to T-cell disease.[58]

The future of lymphoblastic lymphoma treatment for children and young adults

The EURO-LB02 treatment regimen was established as standard of care for lymphoblastic lymphoma and served as the basis for the subsequent international, EICNHL investigator-initiated clinical trial, lymphoblastic lymphoma 2018 (NCT04043494), which was opened for recruitment in 2019 (table 4). Advances in molecular diagnostics have been translated into clinical practice whereby the presence of *FBXW7* and *NOTCH1* mutations in T-cell lymphoblastic lymphoma have been incorporated into risk group stratification in this trial. As lymphoblastic lymphoma is a rare disease, the collaboration of 20 countries with a long tradition of population-based studies is necessary to recruit approximately 680 patients in 5 years.

Anaplastic large cell lymphoma

Clinical achievements for frontline and relapse disease

At the time of its foundation, optimising frontline and relapse therapy for anaplastic large cell lymphoma was one of the main objectives of EICNHL. The BFM protocol, based on a B-cell non-Hodgkin lymphoma strategy, was chosen for further development mainly due to its use of relatively low cumulative doses of therapeutic agents that are associated with long-term toxicity, and a short treatment duration of 5 months. The subsequent EICNHL trial, ALCL99 (NCT00006455), stratifying patients according to clinical risk factors recruited more than 300 patients in 12 countries (table 2). For all patients in the main randomised trial, 3 g/m² methotrexate given as a 3 h infusion without intrathecal triple therapy proved as effective and less toxic than 1 g/m² methotrexate given as a 24 h infusion with intrathecal prophylaxis.[22] The addition of 1 year of weekly vinblastine tested in a randomised setting for patients at high risk resulted in a delay in relapses for the time vinblastine was given but did not improve the 2-year event-free survival.[22] Overall, toxicity was acceptable, and the 2-year event-free survival reached 71% (95% CI 75–77) and overall survival reached 94% (95% CI 89–96), with progression-free survival remaining at 70% after 10 years.[20–23,64] The ALCL99 protocol is now widely used as the standard therapy for paediatric anaplastic large cell lymphoma worldwide (table 2).

Historically, relapse strategies used by each national group within EICNHL have ranged from intensive reinduction chemotherapy followed by autologous or allogeneic haematopoietic stem-cell transplantation (HSCT) to weekly vinblastine monotherapy.[65–67] To our knowledge, the EICNHL-initiated ALCL-Relapse trial (2004–14) is the only population-based international study for a very rare disease conducted to date (table 2). It prospectively tested a risk-adapted approach with all three consolidation approaches according to the risk factors, time to failure and CD3 expression.[27] Of the 105 evaluable relapse-patients included in the trial, event-free survival was 53% (95% CI 48–58) and overall survival was 78% (95% CI 74–82). The survival of children with progression during frontline therapy and those with a relapse of a CD3-positive anaplastic large cell lymphoma was improved compared with the historical control of consolidation with an allogeneic HSCT.[27] However, a high percentage of progressions during reinduction chemotherapy suggests a different reinduction approach is needed. For children with early relapsed CD3-negative anaplastic large cell lymphoma, consolidation by either autologous HSCT after carmustine, etoposide, cytarabine, melphalan (BEAM), and vinblastine was associated with a very high risk of treatment failure, and therefore recommended standard consolidation for patients relapsing within 1 year after diagnosis outside of clinical studies is an allogeneic HSCT. Vinblastine monotherapy for 2 years reached a 5-year event-free survival of 81% (95% CI, 66–100) in children with a late relapse providing a baseline for all future approaches.[27]

Advances in the development of biomarkers to facilitate improvements in treatment outcomes for patients with anaplastic large cell lymphoma

The uniform therapy (ALCL99) of a large patient cohort and international collaboration allowed in-depth analyses of parameters that predict relapse. These included a histological subtype including a small-cell or lympho-histiocytic component,[68] detection of *NPM-ALK* transcripts in bone marrow or blood at diagnosis (MDD) and early during therapy (before the second course of chemotherapy; minimal residual disease [MRD]), or low antibody titres against the ALK fusion protein at diagnosis or at the end of chemotherapy (table 3).[69] Notably, a standardised method for qualitative minimal disease evaluation with regular interlaboratory quality control has been established within EICNHL. This method has allowed validation of MDD and MRD as risk factors in independent patient cohorts.[69] MDD and MRD now constitute standard clinical practice for staging and restaging. Further advances in inter-laboratory standardisation will reveal whether minimal disease quantification, ALK antibody titres or histological subtype, and novel biomarkers such as tumour-derived exosomal cargo might improve risk stratification.[50]

The future of anaplastic large cell lymphoma treatment for children and young adults

Both ALK tyrosine kinase inhibitors and brentuximab vedotin have shown efficacy in treating relapsed anaplastic large cell lymphoma[70,71] and could present low-toxicity alternatives that are also safe for use in reinduction therapy.[27] The ALK inhibitor crizotinib was approved for relapsed anaplastic large cell lymphoma in Europe in November 2022, and so access, which has been limited, should be greatly improved. Three phase 1–2 studies for relapsed anaplastic large cell lymphoma are ongoing: the CRISP trial (NCT00939770) is collecting further information about the safety and efficacy of crizotinib in children, Briga-Ped (EudraCT 2021-002713-34) will test the safety and efficacy of brigatinib, a second generation ALK inhibitor, whereas NivoALCL (EudraCT 2018-001447-31) is assessing the efficacy and consolidation activity of nivolumab in paediatric and adult patients (table 4).

In frontline settings, an EICNHL phase 3 trial will assess the efficacy of vinblastine given once a week for 2 years to children with newly diagnosed, MDD-negative anaplastic large cell lymphoma (EudraCT 2017-002935-40); patients positive for MDD will continue to be treated with the ALCL99 protocol. Patients who are MRD-positive after the first course of ALCL99 are considered to be refractory to treatment and are eligible for inclusion in the aforementioned BrigaPed trial (table 4).

Rare non-Hodgkin lymphomas

Rare childhood non-Hodgkin lymphomas consist of a range of subtypes of B-cell and T-cell origin

Rare paediatric non-Hodgkin lymphomas are often observed in patients with pre-existing conditions and comprise, at most, 10% of childhood non-Hodgkin lymphomas. They include various subtypes of both a B-cell and T-cell origin (panel). Due to the inherently low incidence of rare non-Hodgkin lymphoma subtypes in children and young adults, prospective trials present several challenges and are therefore lacking, as are biological studies.

Panel: Diagnostic entities of rare childhood non-Hodgkin lymphoma

Mature B-lineage:

- Paediatric-type follicular lymphoma
- Paediatric marginal zone lymphoma
- Primary CNS lymphoma

Mature T-lineage:

- Non-anaplastic peripheral T-cell lymphoma not otherwise specified
- Hepatosplenic T-cell lymphoma
- Extranodal natural killer-/T-cell lymphoma: nasal type
- Angioimmunoblastic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Primary cutaneous γδ T-cell lymphoma

Rare non-Hodgkin lymphomas associated with pre-existing conditions

A high incidence of pre-existing conditions is seen in children diagnosed with rarer non-Hodgkin lymphoma subtypes. In a study by Mellgren and colleagues,[72] one in four children developing peripheral T-cell lymphoma had a pre-existing condition, with most having primary or iatrogenic immunodeficiency. Nijmegen breakage syndrome was seen in one in four children developing peripheral T-cell lymphoma not otherwise specified; notably 45% of children developing the very rare hepatosplenic T-cell lymphoma had a pre-existing condition. Similarly, among children developing extranodal marginal zone lymphoma, 27% had a pre-existing condition.[73] Although the majority of these conditions were immunodeficiencies, the association with Sjogren's syndrome, which has been well documented in adults, was also seen. In a study of 14 primary CNS lymphomas, 19% of children had a pre-existing condition.[6] In contrast to the range of histological diagnoses seen throughout the whole cohort, 86% of cases with a pre-existing condition developed diffuse large B-cell lymphoma with just two diagnoses of anaplastic large cell lymphoma. Diagnostic entities of rare childhood non-Hodgkin lymphoma have been shown (panel).

Children with pre-existing conditions have poor treatment outcomes

Children with pre-existing conditions who are diagnosed with non-Hodgkin lymphoma have an inferior outcome than do sporadic cases.[6,24,72] This outcome is probably a

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "paediatric" or "teenage and young adult" and "Non-Hodgkin Lymphoma", "ALCL", "B cell lymphoma", "T cell lymphoma", "peripheral T cell lymphoma", "lymphoblastic lymphoma", "Burkitt lymphoma", "Diffuse large B cell lymphoma" and "Primary Mediastinal large B-cell lymphoma" published in English from Jan 1, 1995 until June 30, 2022. Articles were also identified through searches of the authors' own files. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review. References were selected for their importance, ease of access, and for the further reading opportunities they provide.

result of a combination of increased treatment-related toxicity and high rates of relapse as compared with patients with non-Hodgkin lymphomas without pre-existing conditions. These patients might require enhanced vigilance when receiving standard chemotherapy, modified or reduced-intensity chemotherapy, or when undergoing allogeneic HSCT.[6] Among many questions relevant to the pathogenesis and management of non-Hodgkin lymphomas in the context of pre-existing disease, and especially that seen in children with immunodeficiency, identifying predictors of treatment toxicity and developing increasingly tolerable therapies remains a key goal.[74]

Treatment approaches for children and young adults with rare non-Hodgkin lymphomas

During the past 10 years, EICNHL have done retrospective studies of rare non-Hodgkin lymphomas in collaboration with the international Berlin-Frankfurt-Munster non-Hodgkin lymphoma Committee. This collaboration has led to the development of internationally accepted treatment recommendations: for localised paediatric-type follicular lymphoma and marginal zone lymphoma a watch-and-wait strategy after complete resection is the therapy of choice, whereas for more locally advanced or disseminated stages, low-intensity chemotherapy and immunotherapy, such as anthracycline-free but rituximab-containing courses of rituximab, cyclophosphamide, vincristine, and prednisolone, or rituximab, cyclophosphamide, vinblastine, and prednisolone as used for mature B-cell non-Hodgkin lymphomas should be considered. Treatment recommendations for non-anaplastic peripheral T-cell lymphoma are diverse and range from a moderately intense block-like anaplastic large cell lymphoma-derived regimen (due to improved tolerability compared with regimens adapted for lymphoblastic lymphoma or acute lymphoblastic leukaemia) for peripheral T-cell lymphoma not otherwise specified and subcutaneous panniculitis-like T-cell lymphoma, to a block-like mature B-cell non-Hodgkin lymphoma-derived or anaplastic large cell lymphoma-derived regimen followed by allogeneic or autologous HSCT in first complete remission for hepatosplenic T-cell lymphoma and angioimmunoblastic T-cell lymphoma.[25,72,73,75]

Conclusions and future perspectives

EICNHL together with other collaborative groups (iBFM, COG, Japan, Australia, and New Zealand), has made a considerable difference in the diagnosis, treatment, and survival of paediatric patients with non-Hodgkin lymphoma. Moreover, biological and translational research has revealed several new diagnostic markers important for treatment allocation, disease monitoring, and prognosis. Although prognosis for the different non-Hodgkin lymphoma subtypes has improved, relapses still occur and morbidity and deaths due to early and late toxicity are not rare. These patient outcomes provide the motivation to move forward with collaboration and research to establish new platforms for the treatment of children and young adults with non-Hodgkin lymphomas. EICNHL will continue to work together alongside initiatives such as the ACCELERATE platform in collaboration with academia, pharmaceutical companies, regulatory agencies, and patient advocates to improve the lives of children diagnosed with non-Hodgkin lymphomas. Biological studies within clinical trials will provide a platform to develop non-invasive biomarkers and personalised therapeutics towards improved outcomes.

Contributors

AB was responsible for conceptualisation. All authors wrote the original draft. ST, AB, AA, KM, WW, EM, and VM-C wrote the Review and edited it.

Declaration of interests

LB has sat on advisory boards for the BrigaPed study for Takeda and has received support from Bristol Myers Squibb for the nivoALCL clinical trial. GAAB has received institutional payments for consultancies from Novartis, Roche, Takeda, straZeneca, and Janssen. AA has sat on a board for MSD. All other authors have no competing interests.

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