



Published in final edited form as:

Br J Haematol. 2016 May ; 173(4): 617–624. doi:10.1111/bjh.14009.

Paediatric non-Hodgkin lymphoma - perspectives in translational biology

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Summary

Exciting advances have been achieved for infants, children and adolescents diagnosed with, and treated for, non-Hodgkin lymphoma (NHL). In spite of these successes, new frontiers are being paved to improve the prognosis for those who relapse or have resistant disease. This review summarizes some of the novel approaches and ideas in NHL monitoring, diagnosis and treatment as discussed at the 5th International Symposium on Childhood, Adolescent and Young Adult Non-Hodgkin Lymphoma on October 22nd to 24th 2015 in Varese, Italy.

Keywords

non-Hodgkin lymphoma; lymphoma; childhood lymphoma

Introduction

The prognosis for infants, children and adolescents diagnosed with non-Hodgkin lymphoma (NHL) has significantly improved over the last 2 decades. However 10–30% of these patients will relapse. While there are treatment options available for those patients whose disease recurs, the outcomes remain dismal. Thus therapy strategies focusing on recurrent

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All authors declare no conflicts of interest.

disease present further challenges. Future successes in the treatment, prognosis and understanding paediatric NHL will rely, amongst other factors, on improvements in monitoring for minimal disseminated disease (MDD) and/or minimal residual disease (MRD) and advances in molecular diagnosis which could lead to more molecular and/or immunotargeted therapy. This review will highlight advances in paediatric and adolescent NHL with an emphasis on future strategies and research directions.

Molecular monitoring of disease activity and tumour burden

In children with lymphoblastic leukaemia, examination of the bone marrow (BM) at diagnosis and during therapy is an integral part of their clinical management. The prognostic impact of treatment response overrides other clinical risk factors. MRD is defined as the residual disease detectable in patient's BM or peripheral blood below the detection limit of the available conventional methods. In leukaemia patients, MRD monitoring is currently considered the most reliable strategy to evaluate early treatment response and to refine stratification accordingly (Bhojwani and Pui 2013, Cave, *et al* 1998, Pui, *et al* 2012, Tallen, *et al* 2010).

Several techniques have been developed over the past 15 years to complement morphology in assessing response to treatment, especially MRD, including immunological, molecular and fluorescent in situ hybridization (FISH) assays (Cazzaniga, *et al* 2002, Neale, *et al* 2003, Szczepanski, *et al* 2010). However, most of these techniques have limited sensitivity or applicability. Reliable techniques to detect MRD should discriminate between malignant and normal cells, the tumour-specific markers should be stable and they should have a sensitivity of at least 10^{-4} (1 malignant cell within 10^4 normal cells). The established methods for MRD detection in leukaemia include flow cytometric analysis of aberrant immunophenotypes, polymerase chain reaction (PCR) amplification of fusion transcripts or antigen receptor genes.

MRD could not be assessed in NHL for a long time because markers often need to be developed from the primary tumour. However, fresh material is often not available and MDD-detection is a prerequisite for MRD-measurement in NHL. During the last few years, different studies have demonstrated that MDD and MRD in paediatric NHL could be a powerful tool for stratifying patients in different prognostic groups and monitoring the treatment response (Agsalda, *et al* 2009, Coustan-Smith, *et al* 2009, Damm-Welk, *et al* 2007, Damm-Welk, *et al* 2014, Mussolin, *et al* 2013, Mussolin, *et al* 2011).

The methodologies, timing of MRD assessment and sensitivity required for informative MDD/MRD studies depend mainly on the NHL subtype and clinical question, and also on the expertise and the facilities available. Standardization and inter-laboratory quality control of these methods are absolutely needed to use biological stratification criteria in international studies. In most NHL protocols to date, the treatment plan was not adapted to biological risk factors but rather stage and tumour burden. Anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) is a good example for which biological criteria are becoming an integral part of the management of patients. Until recently, BM involvement was considered a rare event in ALCL, due to the subtle nature of

the BM involvement and the difficulty of its detection by routine morphological examination. Ninety per cent of ALK-positive ALCL carry the t(2;5)(p23;q35) chromosomal translocation, which gives rise to the fusion gene *NPM1-ALK*. The fusion gene transcript can be readily and sensitively detected by PCR. An international study performed in a large cohort of uniformly treated children with ALK-positive ALCL demonstrated MDD-positivity detected by PCR at diagnosis in BM or peripheral blood, in 59% of the patients. MDD-positivity conferred a relapse risk of about 50% (Mussolin *et al*, 2013). Only MDD positivity together with low antibody titre anti-ALK and histology other than common type were predictive of higher risk of failure (hazard ratio 4.9 and 2.7, respectively) in multivariate analysis (Mussolin *et al*, 2013). Furthermore, the persistence of MRD early during treatment identified patients with a very high risk of relapse (80%) (Damm-Welk, *et al* 2014). These studies led to the decision to use MDD for risk stratification in the next ALCL protocol of the European Intergroup for Childhood non-Hodgkin Lymphoma (EICNHL) with risk -adapted therapy. MDD is measured in five national laboratories according to standard operating procedures (SOPs) and routine quality control for *NPM1-ALK* reverse transcription (RT)-PCR measurement has been successfully established among these reference laboratories. This effort is fundamental to ensure reproducible results within multicentre international studies. Newly developed technologies, such as next generation sequencing and digital PCR, which present benefits for MRD/MDD detection still need to demonstrate their technical advantage compared to the established assays before a switch in technology seems reasonable.

The latest data from gene expression profiling, single nucleotide polymorphism arrays and, more recently, next generation sequencing, have expanded the full repertoire of genetic lesions in childhood NHL (Basso, *et al* 2011, Bonn, *et al* 2015, Salaverria, *et al* 2008). T-lymphoblastic lymphoma (T-LBL) is the leading disease entity that highlights this issue. Although many of the genomic studies have increased our knowledge of the pathogenesis of T-LBL, it is not known yet whether and how new specific genotypes will affect the clinical management of patients with T-LBL. Recent retrospective molecular studies in T-LBL have shown an association of loss of heterozygosity at chromosome 6q (LOH6q), biallelic T-cell receptor- γ deletions and *FBXW7* and *NOTCH1* mutations with outcome (Bonn, *et al* 2013, Callens, *et al* 2012). However, the very first biological prognostic parameter on T-LBL, reported by Coustan-Smith *et al* (2009) in 99 paediatric T-LBL patients, was MDD at diagnosis assessed by flow cytometry. Using a cut-off level of 1%, the 2-year event-free survival (EFS) was 68% for patients with higher levels of disease dissemination versus 91% for those with lower levels (Coustan-Smith, *et al* 2009). The prognostic role of MDD for LBL was recently confirmed in a large Italian cohort of pre-B and T-LBL cases (Mussolin, *et al* 2015).

It is likely that genomics will be translated into a better risk stratification that will allow for tailored therapies in the near future. However, several factors need to be considered before introducing a novel genetic discovery as stratification parameter. These include the treatment context, independent verification in other cohorts and/or prospective clinical trials, and independent prognostic values in multivariate analysis with MDD/MRD.

The St. Jude NHL staging classification for paediatric NHL was developed more than 35 years ago (Murphy 1980). An international multidisciplinary expert panel convened in Frankfurt, Germany, at the Third International Childhood, Adolescent and Young Adult NHL Symposium in 2009 to develop a revised international paediatric NHL staging system (IPNHLSS), addressing limitations of the current paediatric NHL staging system and creating a revised classification. The authors recognized that there is evidence that specific disease characteristics, including MDD, may have relevant influence on outcome and they defined subcategories that recognizes novel technologies for minimal disease quantification in BM and cerebral spinal fluid for future consideration (Rosolen, *et al* 2015). It is important to point out that this new NHL staging allows for data collection but does not change the stage or stratification based on the MDD finding. However it provides for opportunities for future analyses to be considered using the staging data, such as whether MDD might be useful for stratification in other subtypes.

Overall, risk stratification in future NHL clinical trials based on newly identified biological risk categories could provide future tailored treatment strategies to improve survival for high-risk patients while decreasing toxicity for low-risk patients. This can be accomplished through novel molecular diagnostics and characterizing lymphomas in children and adolescents.

Molecular diagnosis and subtyping of lymphomas in children

The technology to generate molecular data of tumour specimen has developed rapidly in recent decades. On one hand, these advances increased the complexity of data generated by using high-throughput technology, such as gene expression arrays and next-generation sequencing. On the other hand, broader applicability of molecular analyses is achieved through expanding access to research data. Furthermore, development of assays that allowed use of small amounts of biomaterial, such as cytological preparations as well as biomaterials of limited quantities from formalin-fixed and paraffin embedded (FFPE) tissues, has increased the spectrum of applicability. This development moved molecular profiling from a basic research tool to clinical application and raised excitement that molecular analysis might achieve two goals: (i) improvement in diagnosis; and (ii) subdivision of entities into clinically relevant subgroups. However, insights into disease characteristics that can be translated into clinical application differ between adult and paediatric lymphomas. This difference is highlighted when differentiating mature aggressive B-cell lymphoma, such as Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL). Molecular diagnosis and subtyping appear more relevant in adults compared to children. In contrast, in T-LBL, molecular-genetic subtyping has almost exclusively been driven forward in paediatric lymphoma.

Molecular diagnosis of mature aggressive B-cell lymphoma

Gene expression profiling has been used in mature aggressive B-cell lymphomas to better define, and thus distinguish, BL and primary mediastinal large B-cell lymphoma (PMBCL) from DLBCL, because occasional overlap in morphology, immunophenotype and genetics might occur (Dave, *et al* 2006, Hummel, *et al* 2006, Rosenwald, *et al* 2003). The molecular

classification, in fact has led to a number of re-classifications when compared to the conventional histopathological and immunophenotypical diagnosis. Whether molecular diagnosis does translate into an advantage for the patient has never been proven because all published studies are retrospective. Nevertheless, gene expression analysis has helped to refine disease definitions and the refined definition can be easily applied in patient care. Examples of such new definitions based on gene expression profiling and translated into patient care are: (i) “double hit” lymphomas harbouring both *MYC*- and *BCL2*- or *BCL6*-translocations shown to be distinct from BL (Hummel, *et al* 2006); (ii) a group of lymphomas lacking *MYC*-translocations and aberrations in *11q* share a molecular signature with BL (Salaverria, *et al* 2014); (iii) *BCL2* protein expression might, in fact, be acceptable for the diagnosis of BL (Masque-Soler, *et al* 2015); and (iv) PMBCL might also occur outside of the mediastinum (Yuan, *et al* 2015). Using gene expression profiling to better define a disease and develop new criteria for conventional diagnostic techniques, such as morphology, immunophenotyping, FISH and targeted sequencing, might be a useful approach to translate findings into patient care. In the latter scenario, pressure regarding quality and amount of biomaterial, as well as availability and time prevent the application of sophisticated molecular technology.

Nevertheless, the transfer of gene expression based signatures into an assay that is applicable to FFPE tissue has been demonstrated previously by developing assays for molecular diagnosis and subtyping of DLBCL into the germinal centre-like (GCB) and activated B-cell like (ABC) subtypes. Immunohistochemical classifiers have an error rate that limits their application for treatment options (Meyer, *et al* 2011). Nevertheless, the distinction between both subtypes within DLBCL is likely to become relevant in adult DLBCL given that several drugs have been developed which might be effective in only one of the subtypes (Sehn and Gascoyne 2015). However, whether subtyping of DLBCL is going to be relevant in young patients remains controversial. In contrast to adults, DLBCL in children and adolescents is relatively homogeneous in molecular subtype, with a predominance of GCB (Oschlies, *et al* 2006) and have an excellent outcome using current treatment strategies. Thus, there is less pressure to introduce new subtype-specific substances into the primary therapy compared to adults. Given the high cure rates with conventional chemotherapy it seems unlikely that targeted therapy which requires molecular subtyping of DLBCL will be introduced into the primary therapy of mature aggressive B-cell lymphoma in children and adolescents. However, the poor outcome of some of these lymphomas at relapse is probably prompting physicians to order tests for molecular subtyping in order to detect possible specifically targetable pathways.

Genetic subtyping of lymphoblastic lymphoma

The development of molecular biomarkers for subgroups in T-LBL has almost exclusively been driven by translational research in paediatric lymphoma, primarily because the disease is relatively rare in adult patients. If precursor T-cell neoplasias occur in adults, they usually present as leukaemia and rarely as lymphoma. However, in children, T-LBL represents the second most common lymphoma entity. The development of biomarkers is driven by the need for risk stratification prior to initial therapy due to the high treatment-associated mortality and low survival rates for relapsed patients. Despite the fact that the World Health

Organization (WHO) classification still considers T-LBL and T-cell acute lymphoblastic leukaemia (T-ALL) as one entity (Swerdlow *et al* 2008), there is increasing evidence that T-LBL and T-ALL differ in relevant biological features (Burkhardt, 2010). Therefore, genetic risk scores were developed specifically for T-LBL that differ from the score developed for T-ALL. One recent analysis provided evidence that the mutational status of *NOTCH1/FBXW7* defined a good prognostic subgroup (Callens, *et al* 2012). The recently developed score by Balbach, *et al* (2015) defined a good-risk group (38.5% of patients with a cumulative incidence of relapse of $11\pm 5\%$, *NOTCH1* mutation and no RAS or PIK3–AKT pathway mutation), a high-risk group (15.4% of patients, *NOTCH1* wild type in combination with *PTEN* mutation and loss of heterozygosity at 6q-positive patients) and an intermediate-risk group, which included patients who had neither low- nor high-risk criteria. Despite the fact that the genetically defined risk groups differ slightly between the published studies (Callens *et al*, 2012; Balbach *et al*, 2015) it seems likely that a genetic definition of risk profiles in T-LBL will guide the choice of therapy in future trials.

Advancements in novel molecular diagnostic techniques to characterize paediatric lymphomas provide unique opportunities that influence the ability to match newer agents to these new findings. However, the picture becomes more and more complex, as new sequencing technology provides insights into intratumoral heterogeneity by detection of minor subclones that will require new definitions of genotypes.

Immunological therapy in relation to paediatric non-Hodgkin lymphoma biology

Development of treatment for NHL in children and adolescents has been a paediatric oncology success story. EFS rates for NHL in children and adolescents approach 90% for mature B-NHL (BL and DLBCL), 80% for lymphoblastic lymphomas and 70% for ALCL (Minard-Colin, *et al* 2015). This success is mainly based on the increased understanding of lymphoma biology, description of NHL subtypes, development of risk factors for patient stratification, optimization of subtype-specific poly-chemotherapy regimens and collaboration of study groups worldwide. However, chemotherapy development has reached its limits for the main subgroups. Non-relapse mortality is close to the relapse rate in high-risk BL patients. Studies that analysed less toxic therapy for high risk BL showed an increase in relapses and lymphoma-associated death in those children treated with less intensive chemotherapy. (Cairo, *et al* 2007, Woessmann, *et al* 2005). In addition, these trials demonstrated less intensive therapy was equally effective in the standard risk group but a more dose intensive approach improved outcome in the high-risk group. Intensification of therapy did not improve survival for children with ALCL (Alexander, *et al* 2014, Le Deley, *et al* 2010).

These observations suggest that new treatment options need to be explored for children with NHL. One option is targeted therapies, aiming to inhibit molecular pathways crucial for lymphoma growth and survival. With unravelling of B-cell lymphoma biology and B-cell receptor signalling, a whole array of targeted drugs is being developed for the treatment of mature B-NHL (Mehta-Shah and Younes 2015). However, these drugs have yet to be tested

in children with NHL due to the different B NHL-subtypes in children and the very low number of relapse patients available for Phase I/II studies (e.g., Europe <15 BL relapses/year). International collaborative efforts are necessary to prioritize drugs and explore one new drug after another. It is not possible to accrue enough patients to study several drugs at the same time. In addition, new statistical approaches designed to address the small number of patients are challenges that need to be accepted by pharmaceutical companies and regulatory agencies.

One key example of targeted drugs for childhood NHL is the ALK-kinase inhibitors crizotinib and ceritinib for treatment of ALK-positive ALCL. Their development was driven by the detection of ALK-positive non-small cell lung cancers because ALK-positive ALCL is considered an orphan disease, with only 80 new paediatric cases diagnosed in Europe each year with 16 relapse events. ALK-positive ALCL may, however, be the only tumour that completely depends on activated ALK-signalling. Consequently, almost all children and adults with relapsed ALK-positive ALCL achieved a remission with crizotinib monotherapy (Gambacorti Passerini, *et al* 2014, Mosse, *et al* 2013). However, accumulating evidence suggests that ALK-inhibitors might have to be taken life-long and drug resistance is likely to develop over time. In children, a life-long therapy is difficult to accept in a disease curable in 70% of patients by five months of poly-chemotherapy. Furthermore, long-term therapy with ALK-inhibitors has a huge socio-economic impact and ALK-inhibitors have not been explored for possible late effects, especially in the growing organism. The combination of an ALK-inhibitor with chemotherapy is currently being explored in children in a randomized trial (Children's Oncology Group, ANHL12P1, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01979536) Identifier: NCT01979536).

These data and approaches suggest that the development of targeted therapies for childhood and adolescent NHL might be a long-lasting process that is unlikely to lead to cure for most children. Reaching a cure for paediatric NHL might be achieved by the introduction of yet another treatment option which has emerged as an increasingly powerful tool against tumours during the last decade: immunotherapy. Passive immunotherapy with the anti-CD20 antibody rituximab combined with chemotherapy is now standard of care for adults with aggressive mature B-NHL (Coiffier, *et al* 2002, Pfreundschuh, *et al* 2011) and newer antibodies continue to be explored. Even for rituximab, data in children are still limited to early clinical trials (Goldman, *et al* 2013, Meinhardt, *et al* 2010) with a conformational trial currently underway. The main reasons which inhibited the clinical development of rituximab for children include the high cure rate with standard chemotherapy, the unknown possible late effects on the developing immune system of children and the different paediatric NHL-subtypes compared to adults. The anti-CD30 immunotoxin, brentuximab vedotin, is currently licensed for the treatment of adults with relapsed Hodgkin lymphoma or ALCL. The first study in children (company-sponsored international trial C25002, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01492088) Identifier NCT01492088 including cases in the United States, France, Germany, Italy, Mexico, Netherlands, Spain and United Kingdom) is still enrolling patients and is challenged due to the low number of children with ALCL-relapses available. The Children's Oncology Group is currently enrolling in a randomized Phase II front line study adding brentuximab vedotin to standard chemotherapy for ALCL (ANHL12P1, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01979536) Identifier: NCT01979536).

Autologous cytotoxic T-cell therapy was developed with naturally occurring anti-tumour lymphocytes in adults (Rosenberg and Restifo 2015). T cells engineered to express third generation chimeric antigen receptors (CAR) against CD19 has very successfully opened this application to children with relapsed/refractory ALL (Grupp, *et al* 2013, Lee, *et al* 2015, Maude, *et al* 2014) and should be further tested for the treatment of refractory B-NHL. As an intermediate between antibody and CTL, the BiTE® blinatumomab attracts T cells to CD19 positive cells. This approach – like CAR T-cells – has achieved astonishing responses in adults and some children with refractory precursor B-cell leukaemia (Hoffman and Gore 2014, Schlegel, *et al* 2014). However, its activity in childhood mature B-NHL is not yet known.

Active immunotherapy and stimulation of the patient's anti-tumour immune response opens a new concept of cure for cancer in that the immune system controls a tumour and can lead to final tumour elimination. Anti-idiotypic vaccination has been pursued for chronic lymphocytic leukaemia; however, its application against the highly proliferative childhood B-NHL is limited. Among childhood NHL, ALK-positive ALCL is exquisitely amenable to active immunotherapeutic approaches. Pathological, laboratory and clinical hints suggest that ALCL may provoke an immune response in patients. ALCL cells often are surrounded abundant reactive bystander T cells. Pro-inflammatory cytokines can be detected in the serum of ALCL patients at diagnosis (Mellgren, *et al* 2012). The high efficacy of allogeneic blood stem cell transplantation against relapsed ALCL suggests that a graft-versus ALCL effect may exist (Fukano, *et al* 2015, Gross, *et al* 2010, Strullu, *et al* 2015, Woessmann, *et al* 2006). During the 2000s, two groups described that patients with ALK-positive ALCL mount an immune response against the oncogenic ALK protein. Pulford *et al* (2000) first detected ALK-specific antibodies in the serum of patients with ALK-positive ALCL. ALK-reactive CD8 positive T cells were detected in the T cell repertoire of healthy persons (Passoni, *et al* 2002). Patients with ALK-positive ALCL mount a CD8 and CD4 positive T cell response against ALK (Ait-Tahar, *et al* 2007, Ait-Tahar, *et al* 2006, Passoni, *et al* 2006). The efficacy of an ALK-cDNA-based vaccination in a mouse model of ALK-positive ALCL suggests that an active immunological approach might be clinically relevant (Chiarle *et al* 2008). The systematic analysis of ALK-antibodies titres at diagnosis in children and adolescents with ALK-positive ALCL revealed that the titre of the ALK-antibody inversely correlates with relapse risk (Ait-Tahar, *et al* 2010, Mussolin, *et al* 2013). These findings suggest that the immune response against ALK might be implicated in the final control of human ALCL. The existence of ALCL and observation of inter-individual differences in the strength of the patient's immune response suggest that ALCL employs immune escape mechanisms. One factor with possible therapeutic implications is the NPM1-ALK driven expression of PD-L1 (also termed PDCD1) (Marzec, *et al* 2008). Host factors influencing the immune response are under investigation. The observation that more girls with ALCL mount a high antibody titre compared to boys hints towards an influence of host factors in the immune response as well (Ait-Tahar, *et al* 2010). Current research focuses on further characterization of the patients humoral and cellular immune response against ALK as a prerequisite to develop a clinical vaccination or T cell therapy against ALK.

In summary, despite high survival rates reached by intensive poly-chemotherapy for children with NHL, cure for all, or at least most, children with acceptable side effects and late

morbidity needs collaborative efforts of preclinical and clinical researchers. Innovative and targeted treatment options are becoming increasingly available to children and adolescents who are diagnosed with NHL. Numerous approaches combining or substituting current chemotherapy with targeted drugs and immunotherapeutic approaches need to be developed and tested clinically against NHL in children during the next decades. By influencing and translating advances in molecular characteristics of tumour presentation, therapy strategies can be developed upfront and for recurrent disease. Additional impact on improving outcome can be achieved through monitoring for MDD/MRD through unified efforts internationally. Some elements of translational research discussed in this article and at the 5th International Symposium on Childhood, Adolescent and Young Adult Non-Hodgkin Lymphoma on October 22nd to 24th 2015 in Varese, Italy are already very close to influencing patient management (Table I). These advances in paediatric lymphoma have been accomplished by the concerted efforts of paediatric NHL cooperative groups globally, which could be a paradigm to achieve successes in other diseases as the prognosis for childhood cancer continues to improve.

Acknowledgments

Paediatric lymphoma research of WK is supported by the Kinderkrebs-Initiative Buchholz, Holm-Seppensen (KKI). BS is supported in part by USA NIH grant #U54MD007584. LM is supported in part by Fondazione [CA.RI.PA.RO](#) (grant#13/06). Supported in part by the Paediatric Cancer Research Foundation and Fondazione Giacomo Ascoli.

All authors performed literature search, wrote the manuscript and approved the final version for publication.

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Table I

Translational Research Topics of Likely Relevance for Future Patient Management

	Molecular monitoring of disease activity and tumour burden	Molecular diagnosis and subtyping of NHL in children	Immunological therapy in relation to paediatric NHL biology
LBL	moderate	high	low
BL/DLBCL	moderate	low	high
ALCL	high	low	high

LBL= lymphoblastic (precursor-cell) lymphoma, BL= Burkitt lymphoma, DLBCL= diffuse large B-cell lymphoma, ALCL= anaplastic large cell lymphoma; high= application in current or currently planned clinical trials, moderate= likely to be of relevance in future trials, low= clinical relevance in pediatric lymphoma currently not foreseen.

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