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Children's Oncology Group's 2023 Blueprint for Research: Non-Hodgkin Lymphoma

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Abstract

Pediatric non-Hodgkin lymphoma includes over 30 histologies (many with subtypes), with approximately 800 cases per year in the US. Improvements in survival in NHL over the past 5 decades align with the overall success of the cooperative trial model with dramatic improvements in outcomes. As an example, survival for advanced Burkitt lymphoma is now > 95%. Major remaining challenges include survival for relapsed and refractory disease and long-term morbidity in NHL survivors. Langerhans cell histiocytosis (LCH) was added to the NHL Committee portfolio in recognition of LCH as a neoplastic disorder and the tremendous unmet need for improved outcomes. The goal of the COG NHL Committee is to identify optimal cures for every child and young adult with NHL (and LCH). Further advances will require creative solutions,

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Conflicts of Interest

CEA: Scientific Advisory Board for Sobi, OPNA; Research support from Genentech, Sobi, Day One.
MLH: External Advisory Board for Sobi.
LGR: Scientific Advisory Board for Merck (fees paid to Weill Cornell), Scientific Advisory Board for Roche.
SA, NKE, MF, RJH, EJL, BW: None

including engineering study groups to combine rare populations, biology-based eligibility, alternative endpoints, facilitating international collaborations and coordinated correlative biology.

Keywords

Non-Hodgkin lymphoma; Langerhans cell histiocytosis; clinical trial; pediatric oncology

Introduction

Non-Hodgkin lymphoma (NHL) includes all lymphomas that share the feature of not being Hodgkin lymphoma. This nomenclature unifies a heterogeneous group of disorders under the NHL umbrella.[1] There are approximately 800 cases of pediatric NHL in the United States annually, compared to over 60,000 cases of adult NHL.[2] In children, NHL typically arise due to accidents of immune maturation, and are more common in children with immune disorders.[3] With relatively few cases, and over 30 subtypes, an international pediatric cancer consortium such as the Children's Oncology Group (COG) is essential to organize studies to improve outcomes for children and young adults with NHL (Table 1, Figure 1). As with other pediatric cancers, the COG NHL experience highlights many success stories (Table 2). However, many challenges for children and young adults with NHL remain, including very poor outcomes for patients with relapsed and refractory disease, and long-term consequences of intense chemotherapy.[4] The explosion in targeted and cellular therapies and biology-based risk stratification provide opportunities beyond continued dose-escalation of chemotherapy. Our new challenge is prioritizing and testing new agents in fractionated patient sub-groups.

Mature B cell lymphoma

State of Disease

CAYA with mature B cell lymphoma, including Burkitt lymphoma (BL), diffuse large B cell lymphoma (DLBCL), and gray-zone mature B-cell histological entities, have an excellent outcomes when treated with dose intensive regimens, regardless of stage.[5,6] Risk stratification is based on clinical staging and lactate dehydrogenase (LDH) levels. Identification of biological factors to predict outcome in pediatric mature B-cell NHL remains an unmet need. Recently, somatic p53 alterations have also been associated with poorer outcomes.[7] Measures of minimal disseminated disease (MDD) or minimal residual disease (MRD) have not been found to predict of outcome. The role of disease response measured by PET scan is also a focus of investigation.

Recent Findings

The addition of immunotherapy, specifically the use of the CD20 monoclonal antibody, rituximab, with intensive chemotherapy improves outcomes in higher risk patients. The International B-NHL randomized trial in patients with high-risk mature B-cell lymphoma (stage 3 with elevated LDH or stage 4 disease), (Inter-B-NHL Ritux 2010, COG ANHL1131), demonstrated that the addition of 6 doses of rituximab to intensive LMB/FAB chemotherapy achieved an event-free survival (EFS) of 93.9% in those who received

rituximab, establishing the current standard of care for these patients.[8] This regimen, though highly effective, was associated with short-term toxicity including a high incidence of infection, mucositis and a treatment-related mortality rate of 1.8%. Patients who receive rituximab were also at higher risk for hypogammaglobulinemia one year post completion of therapy.

Patients with relapsed and refractory mature B-NHL have an extremely poor prognosis.[9] The recent SPARKLE trial evaluated the addition of ibrutinib plus RICE or RVICI in patients with relapsed and refractory mature B-cell NHL. The study accrued 65 patients over 5 years in a study involving 94 sites across 21 countries, but failed to show an improvement in outcome.[10] An international phase 2 CD19 chimeric antigen receptor T cell (CAR-T) study using tisaleungeucel demonstrated feasibility of treating patients with this modality, with overall response 32%, and only 7% of patients had a complete response (NCT03610724).

Strategic Opportunities

There are multiple potential novel therapies in development and testing including CD20 (or CD19)/CD3 bispecific T cell engagers (BITEs), antibody drug conjugates and CAR-T constructs that may improve outcomes in patients with relapsed or refractory disease.[11] Future studies will focus on understanding biology with the potential to inform risk stratification, demonstrating safety and efficacy of novel immunotherapies in patients with relapsed or refractory disease, followed by studies designed to preserve or improve the efficacy of primary therapy by decreasing exposures to conventional chemotherapy in lower risk patients and by replacing components of conventional chemotherapy with less toxic immunotherapies. The vanishingly small number of patients with relapsed and refractory disease make large-scale (e.g. national or international) trials essential for this population.

Lymphoblastic Lymphoma

State of Disease

Lymphoblastic lymphoma (LBL) accounts for 25% of pediatric NHL: T-lymphoblastic lymphoma (T-LBL) comprises 70–80% of cases, while precursor B-lymphoblastic lymphoma (pB-LBL) makes up the remaining 20–25% of cases.[12–14] Staging for LBL uses the Murphy classification [15]. Typically, B-LBL presents as localized disease (Murphy stage I&II) while T-LBL generally present as stage III & IV disease. Challenges in trial accrual for patients with B-LBL has limited the ability to assess stage on outcome[16,17]. For patients with T-LBL, advancements in therapy have diminished the significance of stage as an independent risk factor for outcome. [18,19]. Additionally, little information is known regarding biological or molecular variables correlating to outcome in B-LBL. For both T- and B-LBL, clinical distinction between acute lymphoblastic leukemia (ALL) and LBL relies upon the arbitrary cut-off of greater or less than 25% lymphoblast involvement in the bone marrow, respectively. This led to including T- or B-LBL with T- and B-ALL in COG clinical trials. A benefit of this integration was doubling of enrollments for LBL patients compared to past trials.

Recent Findings

Outcomes patients with B-LBL presenting with localized disease are excellent[16]. Recent studies with Capizzi based therapy with asparaginase for patients with T-LBL have increased the OS to approximately 90%. The recent AALL1231 COG study demonstrated the efficacy of bortezomib in patients with T-LBL but not T-ALL, raising the possibility that these conditions have some distinct biological features.[19] For T-LBL, MDD, detected by flow cytometry in the bone marrow at diagnosis, was initially associated with poor outcome [20]. However, more recent studies emphasizing Capizzi based/asparaginase-heavy therapy diminished the significance of MDD[18] and suggested that end of induction MRD levels of T-LBL cells may correlate with EFS [21]. Management of patients with relapsed or refractory B- and T-LBL remain suboptimal. Daratumomab was found to have activity for T-LBL and may be evaluated in the next frontline COG T-LBL and T-ALL trial [10].

Strategic Opportunities

Priorities for both B and T-LBL are focused on advancing work on the molecular characterization of the diseases. Such efforts will lead to advances such as 1) discerning genetic differences between ALL and LBL; 2) identifying key molecular profiles which correlate to clinical outcome; and 3) identifying targetable loci that can facilitate the advancement of novel agents. The continued effort of identifying new, active agents needs to remain a priority for this disease. Avenues such as immunotherapy, disruption of untested pathways, and mediators to overcome chemotherapy resistance merit investigation.

Anaplastic Large Cell Lymphoma (ALCL)

State of Disease

Anaplastic large cell lymphoma (ALCL) is characterized by neoplastic proliferation of $CD30^+$ lymphoid cells, with frequent expression of anaplastic lymphoma kinase (ALK).[22] While ALCL affects only 2% of adults with NHL, it composes 10–15% of all pediatric NHL. The World Health Organization classifies ALCL into two distinct subgroups based on the chromosomal translocation involving the *ALK* gene: ALK positive (ALK+) and ALK negative (ALK-)[1]. The tyrosine kinase encoded by the ALK fusion protein is the oncogenic driver in pediatric ALCL with greater than 95% of cases ALK+.[22,23] Although central nervous system (CNS) involvement is uncommon, most patients present with advanced disease. Previous clinical trials have explored different treatment regimens for patients with ALCL, but a 30% failure rate still exists despite variations in medications, intensity, and length of treatment.[24–29] For patients who relapse, there is no standard of care; it remains unclear how to incorporate agents that target CD30 or ALK and how to optimize the role of allogeneic hematopoietic stem cell transplant (HSCT).

Recent Findings

COG trial ANHL12P1 determined the tolerability, EFS and OS of adding either brentuximab vedotin (BV; Arm BV) or the ALK inhibitor crizotinib (CZ; Arm CZ) to standard chemotherapy for CAYA with systemic CD30+/ALK+ ALCL[30,31]. Patients randomized to Arm BV (n=68) received 1.8 mg/kg BV on day 1 of each 21-day cycle of chemotherapy, for

a total of 6 cycles. While 14 patients relapsed, none relapsed while on therapy. The 2-year EFS and OS were 79.1% and 97.0%, respectively. Of the 67 patients eligible for toxicity evaluation, 66 completed all six cycles of chemotherapy. There were no toxic deaths and no cases of progressive multifocal leukoencephalopathy syndrome or grade 3 or 4 neuropathy. Patients randomized to Arm CZ (n=69) received crizotinib daily during all 6 cycles of chemotherapy. Fifteen patients relapsed; one patient died. Similar to Arm BV, median time to relapse was 7.4 months from diagnosis with all relapses post chemotherapy completion. The 2-year EFS and OS were 76.8% and 95.2%, respectively. The 66 patients who received crizotinib completed 384 cycles of chemotherapy with no toxic deaths. The addition of crizotinib did result in an unexpected toxicity with 13 patients (19.7%) experiencing a grade 2+ thromboembolic adverse event. ANHL12P1 also evaluated the predictive value of MDD as measured by quantitative reverse transcription polymerase chain reaction (PCR) of *ALK* in peripheral blood at diagnosis. In Arm BV, the 2-year EFS was 89.0% for MDD negative cases but only 52.6% for MDD positive cases. Similarly, in Arm CZ the 2-year EFS was 85.6% for MDD negative cases but only 58.1% for MDD positive cases. These results mirror those found in European studies[32–35] and establish the use of MDD to establish risk groups for patients with ALCL.

Strategic Opportunities

Arm BV of ANHL12P1 establishes a new standard of therapy for ALCL, but many unanswered questions remain due to the numerous active agents in ALCL. The next COG ANHL trial will risk stratify patients using MDD. For standard risk patients (MDD-), we will test whether the combination of BV and an ALK inhibitor while minimizing or avoiding standard chemotherapy can maintain EFS. For high-risk patients (MDD+), we will test whether the addition of an ALK inhibitor and maintenance therapy improve EFS. Additional important questions include utilizing ALK inhibitors to avoid cranial radiation in CNS positive patients and determining whether relapsed patients can be cured without a transplant using targeted agents.

Post-transplant lymphoproliferative diseases (PTLD)

State of Disease

Approximately 150 CAYA are diagnosed with PTLD each year in the USA.[36] Incidence varies by transplanted organ ranging from 2% in renal transplants to up to 20% in multi-organ, lung or intestinal transplants.[37] More than 90% of PTLD after solid organ transplant (SOT) in the CAYA group are associated with the Epstein–Barr virus (EBV) and of B-cell origin.[38]

Due to chronic iatrogenic immunosuppression, EBV+ PTLD typically expresses all latent EBV proteins (latency type III). Patients with PTLD characterized by EBV-driven lymphoproliferation with a latency III EBV activation profile have highly immunogenic disease targetable by immunotherapies. Withdrawal or reduction of immunosuppression is the standard first approach for PTLD, but not always feasible because of risk of graft rejection. Up to 80% of patients with polymorphic and monomorphic PTLD require further therapy.[37] Traditionally, low-dose chemotherapy, more recently with the addition of

rituximab, has been used in the frontline treatment of patients with PTLD. In the COG study ANHL0221, six cycles of low dose cyclophosphamide and prednisone in combination with six doses of rituximab led to a 2-year EFS and OS was 71% and 83%, respectively.[39] The German PED-PTLD-2005 used a risk-adapted design with three doses of rituximab followed by evaluation.[40] Patients with complete response (CR) or partial response (PR) received an additional three doses rituximab while all others received chemotherapy. Outcomes were comparable to ANHL0221 with 2-year EFS 67% and OS of 86%, respectively.

Recent findings

Since a major subset of patients with PTLD have highly immunogenic tumors, several institutions have tested EBV-specific T-cells (EBV-TC) in refractory PTLD with response rates of 50–60%. Based on these results, the COG study ANHL1522 study piloted the use of third party EBV-TC in CAYA SOT recipients with PTLD who did not achieve a CR to 3 doses of rituximab. This study accrued 18 patients; 15 patients received EBV-TC. Using a EBV-TC product bank derived from 14 individuals with varied HLA types, all patients had suitable products available. In newly diagnosed patients without CR to rituximab, EBV-TC showed an ORR of 70%. Including two patients with CR to initial rituximab, the 2- year EFS and OS for newly diagnosed patients were 74.1% and 91.7%, respectively. Results in the relapsed and refractory cohort were worse, with 2-year EFS of 33.3% (NCT02900976). These results support adoptive immunotherapy with EBV-TC in newly diagnosed patients with EBV+ PTLD.

Strategic Opportunities

ANHL1522 demonstrated the feasibility of administering third party EBV-TC. EBV-TC are currently being commercialized and need to be studied further in larger studies such as an increased patient population of PTLD with the potential addition of expanded intrinsic (e.g. primary immune deficiency) as well as acquired (e.g. HIV) immune deficiency-associated EBV-lymphoproliferation. An important sub-set of patients with PTLD remain refractory to EBV-specific therapeutic approaches. While EBV-TC show promise for early PTLD, novel diagnostic tools for risk stratification and more effective therapies for patients with advanced and aggressive PTLD are needed.

Primary Mediastinal B Cell

State of Disease

Primary mediastinal B-cell lymphoma (PMBCL) is a rare NHL subtype with a peak incidence in AYA. Patients with PMBCL have historically been included in pediatric mature B-NHL clinical trials; however, outcomes are inferior compared to patients with DLBCL treated on the same protocol (5yr EFS 66% vs. 85%, $p<0.001$).[41] PMBCL tumors harbor frequent amplifications of 9p24.1 which includes the locus for PD-L1/PD-L2.[42] Tumors are also characterized by an immune microenvironment similar to classic Hodgkin lymphoma.

Recent Findings

The dose adjusted EPOCH-R (DA-EPOCH-R) regimen consisting of etoposide, vincristine, doxorubicin, prednisone, cyclophosphamide, and rituximab, has shown excellent outcomes

in adults in a single center phase II trial.[43] The ANHL1131 international trial evaluated the DA-EPOCH-R regimen in children with newly diagnosed PMBCL.[44] The 4 year EFS among the 46 patients enrolled on this trial was 69.6% (95% CI 55.2–80.9). Phase 1 and 2 trials in adults have studied immune checkpoint blockade for relapsed and refractory PMBCL with encouraging overall response rates which range from 45–70%.[45,46] The PD-1 inhibitor pembrolizumab is now FDA approved in children and adults with relapsed or refractory PMBCL after 2 prior therapies.[47]

Strategic Opportunities

Novel therapies are needed to advance outcomes in PMBCL and obviate the need for mediastinal radiation therapy for patients that cannot be cured with chemotherapy alone. A role for checkpoint inhibition in upfront therapy in PMBCL is also an essential unanswered question. COG is leading a NCTN-wide phase 3 trial evaluating the addition of nivolumab to standard chemo-immunotherapy in children and adult patients with newly diagnosed PMBCL (ANHL1931). This trial was designed in collaboration with adult cooperative groups. The primary objective is to compare PFS in response to standard chemo-immunotherapy vs. chemo-immunotherapy + nivolumab. This trial will also allow us to address several key remaining questions in PMBCL. We will be collecting imaging data to determine the role of interim and end-of-therapy PET-CT in determining outcome. Peripheral blood is being collected to evaluate the role of circulating tumor DNA in defining molecular subtypes and predicting outcome. Tumor specimens are also being banked to evaluate the molecular biology of PMBCL. Lastly, we are planning to include patient reported outcomes to determine the impact of chemotherapy and immune checkpoint blockade on health-related quality of life. This trial is not only addressing unmet needs in PMBCL, but has also created a model for successful collaboration between pediatric and adult oncology groups to advance outcomes in adolescents and young adults.

Rare NHL

State of the Disease

Rare NHL encompasses a range of over 20 tumors that together comprise less than 5% of all NHL diagnoses in pediatric and adolescent patients. The most relevant diseases to pediatric oncology are pediatric follicular lymphoma (pFL) and pediatric nodal marginal zone lymphoma (pNMZ) derived from B cells; and peripheral T cell lymphoma not otherwise specified (PTCL-NOS) and subcutaneous panniculitis-like T cell lymphoma (SPTCL), derived from T cells. NHL from NK cells and rarer forms of T and B-cell lymphomas also exist; some associated with EBV. Some of the extremely rare NHL that have been reported in the pediatric population include primary cutaneous T-cell lymphoid proliferations (e.g. mycosis fungoides, lymphomatoid papulosis, and primary cutaneous ALCL), hepatosplenic gamma-delta T-cell lymphoma, primary cutaneous gamma-delta T-cell lymphoma, extra-nodal NK/T-cell lymphoma (nasal-type), T/NK-cell chronic active EBV, and the systemic EBV+ T-cell lymphoma of childhood. Staging is done by Murphy or International NHL staging, except SPTCL which is staged with a tumor/node/metastasis (TNM) approach.[48] Current outcomes are excellent for pFL and pnMZL.[49,50] For rare peripheral (i.e. mature) T-cell lymphomas, representing a heterogeneous group of histologies, the literature reports a

5 year EFS from 47 +/− 7% and OS 56 +/− 7% and 5 year EFS from 61 +/− 11% and OS 65 +/− 11%.[51,52] Relapses occur early typically within a year of diagnosis. Five year EFS and OS for SPTCL is 74 +/−12% and 78 +/−1%.[52] COG efforts in biological and clinical studies focus on the most common diseases with poorer EFS and OS.

Recent Findings

Results from the ECHELON-2 randomized Phase 3 placebo controlled trial using BV with CHP in adults with mature T-cell lymphomas demonstrated improved EFS and OS in all histologies with a median of 25% CD30 expression.[53] The ANHL12P1 trial for CD30+ ALCL demonstrated that the toxicity profile of ALCL99 backbone chemotherapy with BV was very similar to that of ALCL99 chemotherapy alone.[30] We are considering a PTCL-NOS arm with an upcoming ALCL protocol.

There is no standard therapeutic approach to SPTCL. A germline *HAVCR2* mutation involving T cell immunoglobulin mucin 3 (TIM3) was associated with some cases of SPTCL, and patients with *HAVCR2* mutations have a higher frequency of presenting with HLH that may be treatable with immune suppression.[54,55] The Rare NHL subcommittee and NHL committee propose a panel of genomic studies on all rare NK/T cell lymphomas, including specifically.

Strategic Opportunities

Rare NHL strategic priorities are: (1) developing therapies in a clinical trial setting for common, poor outcome, rare NHL leveraging completed trials for similar diseases with biologic and safety justification; and (2) leveraging clinical trial enrollments to obtain samples for genomic studies thus opening opportunities for targeted therapies, *de novo* or extrapolated from clinical studies in adult patients. Further, the umbrella biology protocol *Project EveryChild* (APEC14B1) facilitates biological investigations to inform opportunities for targeted and personalized therapies for patients with rare cancers, including NHL.

Langerhans Cell Histiocytosis

State of Disease

Langerhans cell histiocytosis (LCH) is a myeloid disorder. Recognition of LCH as a hematologic neoplastic disorder and the unmet need of CAYA with LCH supported inclusion of LCH in COG, and assignment to the NHL committee was based largely on physician phenotype. LCH is arises in 5 children per million annually.[56] Clinical manifestations vary and can range from self-resolving unifocal skin or bone lesions to disseminated disease with multi-organ failure.[57] Classification into high vs. low-risk disease is dependent on the presence or absence of ‘Risk Organ’ involvement (e.g. liver, spleen, and/or bone marrow), reflecting risk of death.[58] A subset of LCH patients (5–25%) will develop a debilitating and progressive neurodegeneration (LCH-ND) that can arise many years after presumed control of systemic disease[59]. Mutually exclusive somatic activating mutations in mitogen-activated protein kinase (MAPK) genes (primarily *BRAF (BRAF-V600E)* and *MAP2K1*) cause persistent MAPK activation in myeloid precursors that drive formation of inflammatory LCH lesions.[57,60,61]

The standard of care for newly diagnosed multisystem LCH (vinblastine/prednisone per the Histiocyte Society LCH III protocol) cures fewer than 50% of patients.[58] While salvage and survival rates are high for low-risk disease, treatment failure and repeated treatment courses are associated with significant morbidity.[62] In LCHIII, 15% of high-risk patients ultimately died.[58] Optimal therapy for recurrent or refractory disease remains undefined. Historically, salvage therapies such as high-dose nucleoside analogs and allogeneic HSCT have been effective for treating refractory or recurrent high-risk disease, but are associated with significant morbidity and high treatment-related mortality.[63,64] Case series report promising responses from lower-dose nucleoside analog monotherapy for relapsed and refractory LCH.[65–67]

Recent Findings

The landscape for treating LCH is rapidly changing due to identification of targetable activating MAPK mutations. Early studies in adults demonstrate very high metabolic response rates and clinical improvement in adults with LCH and related Erdheim-Chester disease with BRAFV600E and MEK inhibition.[68–71] Pediatric series demonstrate similar promising responses.[72,73] However, despite high response rates, MAPK pathway inhibition alone does not appear to be curative.[73–75]

Strategic Approach

The LCH community has missed out on decades of investigation that have catalyzed dramatic improvements in other blood cancers through COG. Identification of LCH as a *bona fide* myeloid neoplastic disorder led to development of the recently opened ANHL2121, the first LCH-specific clinical trial to be opened within COG. ANH2121 will evaluate the response rate and tolerability of a pan-RAF inhibitor (tovorafenib) for relapsed and refractory LCH and will establish a platform for LCH clinical trials in COG. Improving outcomes requires prospective clinical trials to optimize risk-adapted front-line and salvage therapies. Potential approaches may include combination MAPK inhibition with chemotherapy, checkpoint inhibition[76], BH3 inhibition[77,78], or other targeted therapies. Further, preventing and effectively treating LCH-ND remains a major unmet need.

Conclusions

The goal of the COG NHL Committee is to identify optimal cures for every child and young adult with NHL (and LCH). Improvements in survival in NHL over the past 5 decades align with the overall success of the cooperative trial model. However, further advances will require creative solutions. Major remaining challenges include survival for relapsed and refractory disease and long-term morbidity in NHL survivors. Potential solutions include optimizing study groups to account for rare populations (e.g. adult/pediatric collaboration); biology-based eligibility (e.g. NCI-COG MATCH); alternative endpoints (e.g. patient reported outcomes); facilitating international collaborations; and incentivizing coordinated correlative biology. Finally, implementing the most effective treatments globally will ultimately be essential to impact 80% of children and young adults with lymphoma who live in lower- and middle-income countries.[79,80]

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Abbreviations:

ALCL	Anaplastic large cell lymphoma
BITE	Bispecific T cell engager
B-ALL	B cell acute lymphoblastic leukemia
B-LBL	B cell lymphoblastic lymphoma
BL	Burkitt lymphoma
CAR-T	Chimeric antigen receptor T cell
CAYA	Children, adolescents and young adults
CNS	Central nervous system
COG	Children' Oncology Group
CR	Complete response
CZ	Crizotinib
DLBCL	Diffuse large B cell lymphoma
EBV	Epstein-Barr Virus
EBV-TC	EBV-specific T cells
EFS	Event-free survival
H&E	Hematoxylin and eosin
HSCT	Hematopoietic stem cell transplant
LCH	Langerhans cell histiocytosis
LCH-ND	Langerhans cell histiocytosis-associated neurodegeneration
LDH	Lactate dehydrogenase
MAPK	Mitogen-activated protein kinase pathway
MDD	Minimal detectable disease
MRD	Minimal residual disease
NHL	Non-Hodgkin lymphoma

OS	Overall survival
PET-CT	Positron emission tomography
pFL	Pediatric follicular lymphoma
pNMZ	Pediatric nodal marginal zone lymphoma
PMBCL	Primary mediastinal B cell lymphoma
PR	Partial response
PTCL-NOS	Peripheral T cell lymphoma, not otherwise specified
RO	Risk organ
SOT	Solid organ transplant
SPTCL	Subcutaneous panniculitis-like T cell lymphoma
T-ALL	T cell acute lymphoblastic leukemia
T-LBL	T cell lymphoblastic lymphoma
TIM3	T cell immunoglobulin mucin 3
TNM	Tumor/node/metastasis

REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127(20):2375–2390. [PubMed: 26980727]
2. Steliarova-Foucher E, Colombet M, Ries LAG, et al. International incidence of childhood cancer, 2001–10: a population-based registry study. Lancet Oncol 2017;18(6):719–731. [PubMed: 28410997]
3. Attarbaschi A, Carraro E, Abla O, et al. Non-Hodgkin lymphoma and pre-existing conditions: spectrum, clinical characteristics and outcome in 213 children and adolescents. Haematologica 2016;101(12):1581–1591. [PubMed: 27515251]
4. Suh E, Stratton KL, Leisenring WM, et al. Late mortality and chronic health conditions in long-term survivors of early-adolescent and young adult cancers: a retrospective cohort analysis from the Childhood Cancer Survivor Study. Lancet Oncol 2020;21(3):421–435. [PubMed: 32066543]
5. Roschewski M, Staudt LM, Wilson WH. Burkitt's Lymphoma. N Engl J Med 2022;387(12):1111–1122. [PubMed: 36129999]
6. Egan G, Goldman S, Alexander S. Mature B-NHL in children, adolescents and young adults: current therapeutic approach and emerging treatment strategies. Br J Haematol 2019;185(6):1071–1085. [PubMed: 30613948]
7. Newman AM, Zaka M, Zhou P, et al. Genomic abnormalities of TP53 define distinct risk groups of paediatric B-cell non-Hodgkin lymphoma. Leukemia 2022;36(3):781–789. [PubMed: 34675373]
8. Minard-Colin V, Auperin A, Pillon M, et al. Rituximab for High-Risk, Mature B-Cell Non-Hodgkin's Lymphoma in Children. N Engl J Med 2020;382(23):2207–2219. [PubMed: 32492302]
9. Moleti ML, Testi AM, Foa R. Treatment of relapsed/refractory paediatric aggressive B-cell non-Hodgkin lymphoma. Br J Haematol 2020;189(5):826–843. [PubMed: 32141616]
10. Burke GAA, Vinti L, Kabickova E, et al. Ibrutinib plus RICE or RVICI for relapsed/refractory mature B-cell non-Hodgkin lymphoma in children and young adults: SPARKLE trial. Blood Adv 2023;7(4):602–610. [PubMed: 36541957]

11. Harker-Murray PD, Pommert L, Barth MJ. Novel Therapies Potentially Available for Pediatric B-Cell Non-Hodgkin Lymphoma. J Natl Compr Canc Netw 2020;18(8):1125–1134. [PubMed: 32755987]
12. Devine KJ, Fries C, Hermiston M, Wistinghausen B. How I approach B-lymphoblastic lymphoma in children. Pediatr Blood Cancer 2023:e30401. [PubMed: 37158503]
13. Si Lim S, Ford JB, Hermiston ML. How I treat newly diagnosed and refractory T-cell acute lymphoblastic lymphoma in children and young adults. Blood 2023.
14. Temple WC, Mueller S, Hermiston ML, Burkhardt B. Diagnosis and management of lymphoblastic lymphoma in children, adolescents and young adults. Best Pract Res Clin Haematol 2023;36(1):101449. [PubMed: 36907639]
15. Murphy SB, Fairclough DL, Hutchison RE, Berard CW. Non-Hodgkin's lymphomas of childhood: an analysis of the histology, staging, and response to treatment of 338 cases at a single institution. J Clin Oncol 1989;7(2):186–193. [PubMed: 2915234]
16. Termuhlen AM, Smith LM, Perkins SL, et al. Outcome of newly diagnosed children and adolescents with localized lymphoblastic lymphoma treated on Children's Oncology Group trial A5971: a report from the Children's Oncology Group. Pediatr Blood Cancer 2012;59(7):1229–1233. [PubMed: 22488718]
17. Termuhlen AM, Smith LM, Perkins SL, et al. Disseminated lymphoblastic lymphoma in children and adolescents: results of the COG A5971 trial: a report from the Children's Oncology Group. Br J Haematol 2013;162(6):792–801. [PubMed: 23889312]
18. Hayashi RJ, Winter SS, Dunsmore KP, et al. Successful Outcomes of Newly Diagnosed T Lymphoblastic Lymphoma: Results From Children's Oncology Group AALL0434. J Clin Oncol 2020;38(26):3062–3070. [PubMed: 32552472]
19. Teachey DT, Devidas M, Wood BL, et al. Children's Oncology Group Trial AALL1231: A Phase III Clinical Trial Testing Bortezomib in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia and Lymphoma. J Clin Oncol 2022;40(19):2106–2118. [PubMed: 35271306]
20. Coustan-Smith E, Sandlund JT, Perkins SL, et al. Minimal disseminated disease in childhood T-cell lymphoblastic lymphoma: a report from the children's oncology group. J Clin Oncol 2009;27(21):3533–3539. [PubMed: 19546402]
21. Hayashi RJ, Hermiston ML, Teachey DT, et al. Correlation of Minimal Residual Disease (MRD) at the End of Induction (EOI) and Event Free Survival (EFS) in T-Cell Lymphoblastic Lymphoma (T-LL), a Report from the Children's Oncology Group (COG) Trial AALL1231. Blood 2022;140(Supplement 1):6387–6389.
22. Stein H, Foss HD, Durkop H, et al. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood 2000;96(12):3681–3695. [PubMed: 11090048]
23. Perkins SL, Pickering D, Lowe EJ, et al. Childhood anaplastic large cell lymphoma has a high incidence of ALK gene rearrangement as determined by immunohistochemical staining and fluorescent in situ hybridisation: a genetic and pathological correlation. Br J Haematol 2005;131(5):624–627. [PubMed: 16351638]
24. Alexander S, Kraveka JM, Weitzman S, et al. Advanced stage anaplastic large cell lymphoma in children and adolescents: results of ANHL0131, a randomized phase III trial of APO versus a modified regimen with vinblastine: a report from the children's oncology group. Pediatr Blood Cancer 2014;61(12):2236–2242. [PubMed: 25156886]
25. Brugieres L, Le Deley MC, Rosolen A, et al. Impact of the methotrexate administration dose on the need for intrathecal treatment in children and adolescents with anaplastic large-cell lymphoma: results of a randomized trial of the EICNHL Group. J Clin Oncol 2009;27(6):897–903. [PubMed: 19139435]
26. Le Deley MC, Rosolen A, Williams DM, et al. Vinblastine in children and adolescents with high-risk anaplastic large-cell lymphoma: results of the randomized ALCL99-vinblastine trial. J Clin Oncol 2010;28(25):3987–3993. [PubMed: 20679620]
27. Lowe EJ, Sposto R, Perkins SL, et al. Intensive chemotherapy for systemic anaplastic large cell lymphoma in children and adolescents: final results of Children's Cancer Group Study 5941. Pediatr Blood Cancer 2009;52(3):335–339. [PubMed: 18985718]

28. Pillon M, Gregucci F, Lombardi A, et al. Results of AIEOP LNH-97 protocol for the treatment of anaplastic large cell lymphoma of childhood. Pediatr Blood Cancer 2012;59(5):828–833. [PubMed: 22389307]
29. Seidemann K, Tiemann M, Schrappe M, et al. Short-pulse B-non-Hodgkin lymphoma-type chemotherapy is efficacious treatment for pediatric anaplastic large cell lymphoma: a report of the Berlin-Frankfurt-Munster Group Trial NHL-BFM 90. Blood 2001;97(12):3699–3706. [PubMed: 11389005]
30. Lowe EJ, Reilly AF, Lim MS, et al. Brentuximab vedotin in combination with chemotherapy for pediatric patients with ALK+ ALCL: results of COG trial ANHL12P1. Blood 2021;137(26):3595–3603. [PubMed: 33684925]
31. Lowe EJ, Reilly AF, Lim MS, et al. Crizotinib in Combination With Chemotherapy for Pediatric Patients With ALK+ Anaplastic Large-Cell Lymphoma: The Results of Children's Oncology Group Trial ANHL12P1. Journal of Clinical Oncology 2022.
32. Damm-Welk C, Kutscher N, Zimmermann M, et al. Quantification of minimal disseminated disease by quantitative polymerase chain reaction and digital polymerase chain reaction for NPM-ALK as a prognostic factor in children with anaplastic large cell lymphoma. Haematologica 2020;105(8):2141–2149. [PubMed: 31649129]
33. Damm-Welk C, Mussolin L, Zimmermann M, et al. Early assessment of minimal residual disease identifies patients at very high relapse risk in NPM-ALK-positive anaplastic large-cell lymphoma. Blood 2014;123(3):334–337. [PubMed: 24297868]
34. Iijima-Yamashita Y, Mori T, Nakazawa A, et al. Prognostic impact of minimal disseminated disease and immune response to NPM-ALK in Japanese children with ALK-positive anaplastic large cell lymphoma. Int J Hematol 2018;107(2):244–250. [PubMed: 29030834]
35. Mussolin L, Damm-Welk C, Pillon M, et al. Use of minimal disseminated disease and immunity to NPM-ALK antigen to stratify ALK-positive ALCL patients with different prognosis. Leukemia 2013;27(2):416–422. [PubMed: 22907048]
36. Bollard CM, Lim MS, Gross TG, Committee COGN-HL. Children's Oncology Group's 2013 blueprint for research: non-Hodgkin lymphoma. Pediatr Blood Cancer 2013;60(6):979–984. [PubMed: 23255391]
37. Rubinstein J, Toner K, Gross T, Wistinghausen B. Diagnosis and management of post-transplant lymphoproliferative disease following solid organ transplantation in children, adolescents, and young adults. Best Pract Res Clin Haematol 2023;36(1):101446. [PubMed: 36907642]
38. Wistinghausen B, Gross TG, Bollard C. Post-transplant lymphoproliferative disease in pediatric solid organ transplant recipients. Pediatric hematology and oncology 2013;30(6):520–531. [PubMed: 23802715]
39. Gross TG, Orjuela MA, Perkins SL, et al. Low-dose chemotherapy and rituximab for posttransplant lymphoproliferative disease (PTLD): a Children's Oncology Group Report. Am J Transplant 2012;12(11):3069–3075. [PubMed: 22883417]
40. Maecker-Kohlhoff B, Beier R, Zimmermann M, SChlegelberger B, Baumann U, Mueller Cm, Pape L, reiter A, Rossig C, Schubert S, Toenshoff B, Wingen A, Meissner B, Kebelmann-Betzing C, Henze G, Kreipe HH, Klein C. Response-Adapted Sequential Immuno-Chemotherapy of Post-Transplant Lymphoproliferative Disorders in Pediatric Solid Organ Transplant Recipients: Results from the Prospective Ped-PTLD 2005 Trial Abstract presented at American Society of Hematology; December 5, 2014, 2014; San Francisco, CA.
41. Gerrard M, Waxman IM, Sposto R, et al. Outcome and pathologic classification of children and adolescents with mediastinal large B-cell lymphoma treated with FAB/LMB96 mature B-NHL therapy. Blood 2013;121(2):278–285. [PubMed: 23149845]
42. Mottok A, Hung SS, Chavez EA, et al. Integrative genomic analysis identifies key pathogenic mechanisms in primary mediastinal large B-cell lymphoma. Blood 2019;134(10):802–813. [PubMed: 31292115]
43. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. The New England journal of medicine 2013;368(15):1408–1416. [PubMed: 23574119]

44. Burke GAA, Minard-Colin V, Auperin A, et al. Dose-Adjusted Etoposide, Doxorubicin, and Cyclophosphamide With Vincristine and Prednisone Plus Rituximab Therapy in Children and Adolescents With Primary Mediastinal B-Cell Lymphoma: A Multicenter Phase II Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2021;39(33):3716–3724. [PubMed: 34570655]
45. Armand P, Rodig S, Melnichenko V, et al. Pembrolizumab in Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2019;37(34):3291–3299. [PubMed: 31609651]
46. Zinzani PL, Santoro A, Gritti G, et al. Nivolumab Combined With Brentuximab Vedotin for Relapsed/Refractory Primary Mediastinal Large B-Cell Lymphoma: Efficacy and Safety From the Phase II CheckMate 436 Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2019;37(33):3081–3089. [PubMed: 31398081]
47. FDA approves pembrolizumab for treatment of relapsed or refractory PMBCL 2018.
48. Olsen EA, Whittaker S, Willemze R, et al. Primary cutaneous lymphoma: recommendations for clinical trial design and staging update from the ISCL, USCLC, and EORTC. Blood 2022;140(5):419–437. [PubMed: 34758074]
49. Attarbaschi A, Abla O, Arias Padilla L, et al. Rare non-Hodgkin lymphoma of childhood and adolescence: A consensus diagnostic and therapeutic approach to pediatric-type follicular lymphoma, marginal zone lymphoma, and nonanaplastic peripheral T-cell lymphoma. Pediatr Blood Cancer 2020;67(8):e28416. [PubMed: 32452165]
50. O'Suoji C, Welch JJ, Perkins SL, et al. Rare Pediatric Non-Hodgkin Lymphomas: A Report From Children's Oncology Group Study ANHL 04B1. Pediatr Blood Cancer 2016;63(5):794–800. [PubMed: 26728447]
51. Kontny U, Oschlies I, Woessmann W, et al. Non-anaplastic peripheral T-cell lymphoma in children and adolescents--a retrospective analysis of the NHL-BFM study group. Br J Haematol 2015;168(6):835–844. [PubMed: 25395120]
52. Mellgren K, Attarbaschi A, Abla O, et al. Non-anaplastic peripheral T cell lymphoma in children and adolescents-an international review of 143 cases. Ann Hematol 2016;95(8):1295–1305. [PubMed: 27270301]
53. Horwitz S, O'Connor OA, Pro B, et al. The ECHELON-2 Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma. Ann Oncol 2022;33(3):288–298. [PubMed: 34921960]
54. Gayden T, Sepulveda FE, Khuong-Quang DA, et al. Germline HAVCR2 mutations altering TIM-3 characterize subcutaneous panniculitis-like T cell lymphomas with hemophagocytic lymphohistiocytic syndrome. Nat Genet 2018;50(12):1650–1657. [PubMed: 30374066]
55. Polprasert C, Takeuchi Y, Kakiuchi N, et al. Frequent germline mutations of HAVCR2 in sporadic subcutaneous panniculitis-like T-cell lymphoma. Blood Adv 2019;3(4):588–595. [PubMed: 30792187]
56. Rodriguez-Galindo C, Allen CE. Langerhans cell histiocytosis. Blood 2020;135(16):1319–1331. [PubMed: 32106306]
57. Allen CE, Merad M, McClain KL. Langerhans-Cell Histiocytosis. N Engl J Med 2018;379(9):856–868. [PubMed: 30157397]
58. Gadner H, Minkov M, Grois N, et al. Therapy prolongation improves outcome in multisystem Langerhans cell histiocytosis. Blood 2013;121(25):5006–5014. [PubMed: 23589673]
59. McClain KL, Picarsic J, Chakraborty R, et al. CNS Langerhans cell histiocytosis: Common hematopoietic origin for LCH-associated neurodegeneration and mass lesions. Cancer 2018;124(12):2607–2620. [PubMed: 29624648]
60. Badalian-Very G, Vergilio JA, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood 2010;116(11):1919–1923. [PubMed: 20519626]
61. Berres ML, Lim KP, Peters T, et al. BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. J Exp Med 2014;211(4):669–683. [PubMed: 24638167]

62. Haupt R, Nanduri V, Calevo MG, et al. Permanent consequences in Langerhans cell histiocytosis patients: a pilot study from the Histiocyte Society-Late Effects Study Group. Pediatr Blood Cancer 2004;42(5):438–444. [PubMed: 15049016]

63. Bernard F, Thomas C, Bertrand Y, et al. Multi-centre pilot study of 2-chlorodeoxyadenosine and cytosine arabinoside combined chemotherapy in refractory Langerhans cell histiocytosis with haematological dysfunction. Eur J Cancer 2005;41(17):2682–2689. [PubMed: 16291085]

64. Veys PA, Nanduri V, Baker KS, et al. Haematopoietic stem cell transplantation for refractory Langerhans cell histiocytosis: outcome by intensity of conditioning. Br J Haematol 2015;169(5):711–718. [PubMed: 25817915]

65. Abraham A, Alsultan A, Jeng M, Rodriguez-Galindo C, Campbell PK. Clofarabine salvage therapy for refractory high-risk langerhans cell histiocytosis. Pediatr Blood Cancer 2013;60(6):E19–22. [PubMed: 23255383]

66. Simko SJ, Tran HD, Jones J, et al. Clofarabine salvage therapy in refractory multifocal histiocytic disorders, including Langerhans cell histiocytosis, juvenile xanthogranuloma and Rosai-Dorfman disease. Pediatr Blood Cancer 2014;61(3):479–487. [PubMed: 24106153]

67. Simko SJ, McClain KL, Allen CE. Up-front therapy for LCH: is it time to test an alternative to vinblastine/prednisone? Br J Haematol 2015;169(2):299–301. [PubMed: 25400231]

68. Diamond EL, Subbiah V, Lockhart AC, et al. Vemurafenib for BRAF V600-Mutant Erdheim-Chester Disease and Langerhans Cell Histiocytosis: Analysis of Data From the Histology-Independent, Phase 2, Open-label VE-BASKET Study. JAMA Oncol 2018;4(3):384–388. [PubMed: 29188284]

69. Haroche J, Cohen-Aubart F, Emile JF, et al. Reproducible and sustained efficacy of targeted therapy with vemurafenib in patients with BRAF(V600E)-mutated Erdheim-Chester disease. J Clin Oncol 2015;33(5):411–418. [PubMed: 25422482]

70. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. N Engl J Med 2015;373(8):726–736. [PubMed: 26287849]

71. Diamond EL, Durham BH, Ulaner GA, et al. Efficacy of MEK inhibition in patients with histiocytic neoplasms. Nature 2019;567(7749):521–524. [PubMed: 30867592]

72. Eckstein OS, Nuchtern JG, Mallory GB, et al. Management of severe pulmonary Langerhans cell histiocytosis in children. Pediatr Pulmonol 2020;55(8):2074–2081. [PubMed: 32511892]

73. Donadieu J, Larabi IA, Tardieu M, et al. Vemurafenib for Refractory Multisystem Langerhans Cell Histiocytosis in Children: An International Observational Study. J Clin Oncol 2019;37(31):2857–2865. [PubMed: 31513482]

74. Cohen Aubart F, Emile JF, Carrat F, et al. Targeted therapies in 54 patients with Erdheim-Chester disease, including follow-up after interruption (the LOVE study). Blood 2017;130(11):1377–1380. [PubMed: 28667012]

75. Eckstein OS, Visser J, Rodriguez-Galindo C, Allen CE. Clinical responses and persistent BRAF V600E(+) blood cells in children with LCH treated with MAPK pathway inhibition. Blood 2019;133(15):1691–1694. [PubMed: 30718231]

76. Sengal A, Velazquez J, Hahne M, et al. Overcoming T-cell exhaustion in LCH: PD-1 blockade and targeted MAPK inhibition are synergistic in a mouse model of LCH. Blood 2021;137(13):1777–1791. [PubMed: 33075814]

77. Bigenwald C, Le Berichel J, Wilk CM, et al. BRAF(V600E)-induced senescence drives Langerhans cell histiocytosis pathophysiology. Nat Med 2021;27(5):851–861. [PubMed: 33958797]

78. Hogstad B, Berres ML, Chakraborty R, et al. RAF/MEK/extracellular signal-related kinase pathway suppresses dendritic cell migration and traps dendritic cells in Langerhans cell histiocytosis lesions. J Exp Med 2018;215(1):319–336. [PubMed: 29263218]

79. Collaborators GBDAYAC. The global burden of adolescent and young adult cancer in 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Oncol 2022;23(1):27–52. [PubMed: 34871551]

80. Ozuah NW, Lubega J, Allen CE, El-Mallawany NK. Five decades of low intensity and low survival: adapting intensified regimens to cure pediatric Burkitt lymphoma in Africa. Blood Adv 2020;4(16):4007–4019. [PubMed: 32841337]

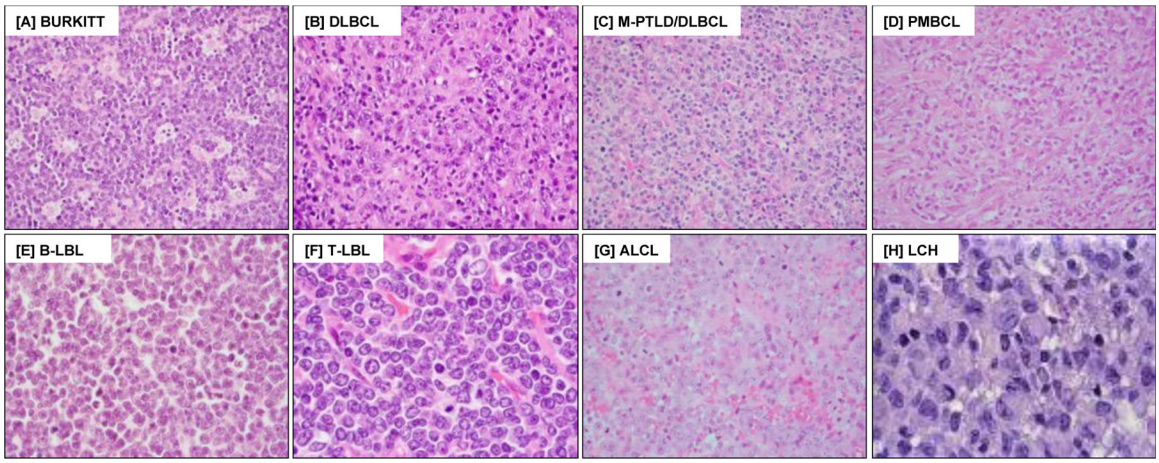

Figure 1. NHL and LCH Histology

[A] BURKITT (Burkitt lymphoma): The neoplastic cells are intermediate-sized and uniform with round to squared-off borders. The nuclei have one to multiple small nucleoli, and there are tingible body macrophages and abundant apoptotic cells in the background. H&E stain. Original magnification 400x.

[B] DLBCL (diffuse large B-cell lymphoma): The neoplastic cells are large with a moderate amount of cytoplasm, irregular to lobulated nuclei, vesicular chromatin, and variably prominent nucleoli. H&E stain. Original magnification 400x.

[C] M-PTLD/DLBCL (monomorphic post-transplant lymphoproliferative disorder with DLBCL histology): The neoplastic cells are intermediate to large with open chromatin and variably prominent nucleoli. There are small lymphocytes and occasional plasma cells in the background. H&E stain. Original magnification 400x.

[D] PMBCL (primary mediastinal B-cell lymphoma): The neoplastic cells are intermediate to large with cleared out cytoplasm. There are thin bands of collagen fibrosis in the background. H&E stain. Original magnification 400x.

[E] B-LBL (B-cell lymphoblastic lymphoma): The neoplastic cells are slightly larger than a normal lymphocyte and have open, pale chromatin and round to slightly irregular nuclear contours. H&E stain. Original magnification 1,000x.

[F] T-LBL (T-cell lymphoblastic lymphoma): The neoplastic cells are slightly larger than a normal lymphocyte and have open, pale chromatin and irregular nuclear contours. H&E stain. Original magnification 1,000x.

[G] ALCL (anaplastic large cell lymphoma): Cells are large and pleomorphic with variably prominent nucleoli. A horseshoe-shaped “hallmark” cell is present near the middle of the image. H&E stain. Original magnification 400x.

[H] LCH (Langerhans cell histiocytosis): Langerhans cells show abundant cytoplasm and nuclei with folds and occasional longitudinal grooves. H&E stain.

Table 1:

Categorization of Non-Hodgkin Lymphomas and Lymphoproliferative Disorders in Children and Adolescents in the Context of Cell Origin and Incidence in the Pediatric Population

CATEGORY	B-CELL COMPARTMENT	T/NK-CELL COMPARTMENT
COMMON	Burkitt Lymphoma	T-cell Lymphoblastic Lymphoma
	Diffuse Large B-cell Lymphoma (DLBCL)	ALK+ Anaplastic Large Cell Lymphoma (ALCL)
	Primary Mediastinal B-cell Lymphoma	
LESS COMMON & RARE	B-cell Lymphoblastic Lymphoma	Peripheral T-cell Lymphoma, NOS
	B-cell PTLD (non-destructive, polymorphic, monomorphic)	ALK-negative ALCL
	High-grade B-cell Lymphoma, NOS	Extranodal NK/T-cell Lymphoma
	High-grade B-cell Lymphoma with 11q Aberrations	Subcutaneous Panniculitis-like T-cell Lymphoma
	High-grade "Double-Hit" B-cell Lymphoma [#]	Hepatosplenic (Gamma-Delta) T-cell Lymphoma
	Large B-cell Lymphoma with *IRF4* Rearrangement	Primary Cutaneous Gamma-Delta T-cell Lymphoma
	T-cell/histiocyte-rich Large B-cell Lymphoma	Mycosis Fungoides
	Mediastinal Gray-Zone Lymphoma [^]	Lymphomatoid Papulosis (Primary Cutaneous CD30+ LPD)
	Pediatric-type Follicular Lymphoma	Primary Cutaneous ALCL (Primary Cutaneous CD30+ LPD)
	Pediatric Nodal Marginal Zone Lymphoma	Angioimmunoblastic T-cell Lymphoma
VERY RARE [*]	Extranodal Marginal Zone Lymphoma	Systemic EBV+ T-cell Lymphoma of Childhood
	EBV+ DLBCL, NOS	T/NK-cell Chronic Active EBV
	Lymphomatoid Granulomatosis	Primary Cutaneous CD4+ Small/Medium T-cell LPD
	Primary CNS Lymphoma	T-large Granular Lymphocytic Leukemia
	Plasmablastic Lymphoma	T-cell PTLD (monomorphic)
	Primary Effusion Lymphoma	Aggressive NK-cell Leukemia
	Multicentric Castleman Disease	Enteropathy-associated T-cell Lymphoma
		Adult T-cell Leukemia/Lymphoma

LEGEND: NK = natural killer, PTLD = post-transplant lymphoproliferative disorders, NOS = not otherwise specified, EBV = Epstein-Barr virus, CNS = central nervous system, LPD = lymphoproliferative disorder.

[#]Also known as: High-grade B-cell lymphoma, with *MYC* and *BCL2* rearrangements (also previously included *BCL6* rearrangements).

[^]Also previously known as: B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma.

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* Please note that numerous additional lymphoma diagnoses exist on the 2022 version of the World Health Organization Classification of Lymphoid Neoplasms, however they are not all included in this table due to the extremely rare nature of their occurrence in children.

Table 2:

Summary of Recent and Current Children's Oncology Group Clinical Trials for Non-Hodgkin Lymphomas and LCH

STUDY	DISEASE	NOVEL AGENT	OUTCOMES	IMPACT
ANHL1131 (Phase III) NCT01516580	Mature B-NHL *Front line*	Rituximab	Addition of rituximab to LMB chemo backbone improved EFS (93.9%)	• Established rituximab + LMB backbone as an internationally accepted standard for high-risk pediatric mature B cell lymphoma.
AALL0434 (Phase III) NCT00408005	T-cell LBL *Front line*	Nelarabine	Addition of nelarabine to augmented BFM T-lymphoblastic regimen did not alter EFS for lymphoma	• Identified potential for differential responses between T-LBL and T-ALL • Confirmed efficacy of asparaginase-heavy Capizzi MTX backbone
AALL1231 (Phase III) NCT02112916	T-cell LBL *Front line*	Bortezomib	Bortezomib arm with superior EFS, higher toxicity with dexamethasone-based induction for lymphoma	• Identified bortezomib as potentially beneficial for T-LBL compared to T-ALL • Supported prednisone-based induction for T-LBL
ADVL0912 (Phase I/II) NCT00939770	ALK+ ALCL *Relapsed/refractory*	Crizotinib	Complete response rates of 83 & 80% for Phase I/II arms (respectively)	• Established activity of single-agent ALK-inhibition in relapsed/ refractory ALK+ ALCL
ANHL12P1 (Phase II) NCT01979536	ALK+ ALCL *Front line*	Brentuximab	Addition of brentuximab to ALCL99 backbone chemo achieved 79.1% EFS with no relapses on therapy	• Established safety of brentuximab with ALCL99 • Established brentuximab + ALCL99 backbone as the current standard of care
ANHL12P1 (Phase II) NCT01979536	ALK+ ALCL *Front line*	Crizotinib	Crizotinib + ALCL99 backbone had similar outcomes as brentuximab, but frequent thrombotic complications	• Comparable responses and OS to brentuximab + ALCL99 • Higher thrombotic complications compared to brentuximab+ALCL99
ANHL1522 (Phase II) NCT02900976	PTLD *Refractory to rituximab*	3rd party EBV-TC	Overall response rate of 70%	• Demonstrated feasibility of cellular therapy for EBV+ PTLD • Responses more frequent in patients with early PTLD
ANHL1131 (Phase II) NCT01516580	PMBCL *Front line*	Rituximab	Rituximab + dose-adjusted EPOCH (DA-EPOCH-R) without XRT resulted in 69.6% EFS	• EFS remained suboptimal, resulting in incorporation of nivolumab to DA-EPOCH-R backbone in current study (ANHL1931).
ANHL1931 (Phase III) NCT04759586	PMBCL *Front line*	Nivolumab	Study open and enrolling	• Collaboration with adult NCCN group partners
AALL1731 & 1732 (Phase III) NCT03914625 & NCT03959085	Localized (1731) & Disseminated (1732) B-cell LBL	None	Study open and enrolling	• Non-randomized treatment according to standard & high-risk B-cell acute lymphoblastic leukemia therapy • Explore prognostic significance of minimal disseminated disease in bone marrow at baseline
ANHL2121 (Phase II) NCT05828069	LCH *Relapsed/refractory*	Tovorafenib	Study open and enrolling	• First LCH study in COG
APEC14B1 (Biology Study) NCT02402244	All	None	Study open and enrolling	• Development of a well annotated childhood cancer biorepository for research through biospecimen collection

LEGEND: B-NHL = B-cell non-Hodgkin lymphomas (ie Burkitt lymphoma, diffuse large B-cell lymphoma, and gray-zone high-grade B-cell lymphomas), LMB = lymphomes malins B (French consortium), chemo = chemotherapy, EFS = event-free survival, LBL = lymphoblastic lymphoma, BFM = Berlin-Frankfurt-Münster consortium, ALL = acute lymphoblastic leukemia, Capizzi MTX = intermediate-dose methotrexate, ALCL = anaplastic large cell lymphoma, PTLD = post-transplant lymphoproliferative disorders, EBV-TC = Epstein-Barr virus-specific cytotoxic T-cell therapy, PMBCL = primary mediastinal B-cell lymphoma, XRT = radiation therapy, LCH=Langerhans cell histiocytosis.

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