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Non-Hodgkin Lymphomas in Childhood: How to Move On?

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SUMMARY
Non-Hodgkin lymphomas of childhood represent a diverse group of neoplasms with different clinical, pathological, immunophenotypical and genetic features. A vast majority of childhood non-Hodgkin lymphomas could be classified into one of the three major histological subgroups: mature B-cell neoplasms, lymphoblastic lymphomas or anaplastic large cell lymphomas. Modern therapeutic strategies lead to cure in more than 80% of patients. Conversely, refractory diseases, as well as disease relapse convey a dismal prognosis. This fact requires much better stratification based on prognostic markers which would ideally recognize distinct groups of patients requiring different therapeutic regimens. Defining novel diagnostic and prognostic markers should improve diagnosis and prognosis as well as patient follow-up. It should also allow introduction of individually tailored treatment regimens in selected groups of patients with non-Hodgkin lymphomas, with the main goal of improving treatment results and decreasing short- and long-term complications.
Keywords: non-Hodgkin lymphoma; children; classification; diagnosis; prognosis; treatment

INTRODUCTION

Lymphomas are neoplasms of lymphoid tissues and organs. Lymphoid tissues include single lymphocytes located in the epithelium of mucous membranes, aggregates of lymphocytes in the skin, gastrointestinal and respiratory tract mucosa, or entire organs (i.e., lymph nodes, thymus and spleen) strategically located near lymphatics and blood vessels. Lymphomas can arise in any lymphoid tissue. If they originate from lymphatic tissues other than lymph nodes, they are referred to as extranodal lymphomas. In general, staging procedures for pediatric non-Hodgkin lymphomas (NHL) include computerized tomography (CT) imaging of the neck, chest, abdomen, and pelvis, bilateral iliac crest bone marrow aspiration and biopsy and examination of cerebrospinal fluid. After performing the abovementioned investigations, pediatric NHL are staged according to the common Murphy's staging system [1].

Pediatric lymphomas are usually classified as either Hodgkin lymphoma (HL) or as non-Hodgkin lymphomas, but they are clinically, pathologically, and biologically different. Specific disease entities are classified according to the cell lineage of origin (i.e., B-lineage and T-lineage or natural killer – NK cells) and also, according to their origin from precursor or mature lymphoid cells. Besides, some types of lymphoma are mainly associated with particular age groups, such as children. Classification of lymphoma has evolved over the past decades from a morphology based scheme to the system that integrates morphological, immunophenotypic, genetic, molecular, and clinical features into categories adopted for use by pathologists, clinicians and basic scientists. World Health Organization (WHO) classification of lymphoid neoplasms published in 2001 and updated in 2008, represents a universal consensus on the diagnosis of about 70 different forms of lymphoma [2]. However, as new discoveries are made, and new insights are gained, these classifications will continue to evolve with possible additional modifications.

LYMPHOMAS OF CHILDHOOD

Cancer in children (0-14 years) and adolescents (15-19 years) is rare, contributing to less than 1% of the total human cancers. For all malignant neoplasms, age-adjusted incidence rate is 140 per million for children and 157 per million for ages 0-19 years in Europe [3].

Lymphomas are the third most common childhood malignancy, preceded only by leukemias and brain tumors. NHL accounts for about 6% of childhood cancer in patients younger than 19 years [3]. The incidence of childhood NHL varies with age, histology, gender, and race. NHL in children is most frequently diagnosed in the second decade of life, infrequently in children younger than 3 years and very rarely in infants [4]. Childhood NHL is more common in males, except for primary mediastinal large B-cell lymphoma, the incidence of which is almost equal between sexes [5]. NHL is rare in Japan but very frequent in the African continent, particularly the "endemic" Burkitt lymphoma.

Childhood NHLs differ from adult NHL regarding disease types, biology, treatment,

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Table 1. Current WHO classification and relative frequency of childhood non-Hodgkin lymphomas (NHL)

NHL type		Relative frequency
Mature B-cell neoplasms	Burkitt lymphoma	40%
	Diffuse large B-cell lymphoma with primary mediastinal large B-cell lymphoma	10%
	B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma	?
Precursor lymphoid neoplasms	T lymphoblastic lymphoma	20–25%
	B lymphoblastic lymphoma	5%
Mature T-cell and NK-cell	Anaplastic large-cell lymphoma	10–15%
Rare subtypes		5–10%

NK – natural killer

and outcome. Contrary to adults where NHL is usually of low or intermediate grade, in children it is usually disseminated, diffuse not nodular, high grade, rapidly growing, originating from mature or immature B and T cells, with frequent extranodal disease, bone marrow and central nervous system (CNS) involvement [2, 6]. Childhood NHLs are heterogeneous, however much less comparing to adult lymphomas. The subtype distribution significantly differs among children and adults. Classification systems used for adult lymphomas are complicated due to numerous diagnoses rarely observed in children. About 90% of childhood NHL can be categorized into three categories, according to WHO classification: 1) mature B cell neoplasms (Burkitt lymphoma/leukemia; B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma; diffuse large B-cell lymphoma (DLBCL) and primary mediastinal (thymic) large B-cell lymphoma; 2) precursor lymphoid neoplasms (B lymphoblastic leukemia/lymphoma and T lymphoblastic leukemia/lymphoma and 3) mature T-cell and NK-cell neoplasms (anaplastic large-cell lymphoma – ALCL). Other types, rarely seen in children, account for about 10% (Table 1) [7].

Treatment results of pediatric lymphomas were extremely poor a few decades ago. Owing to current treatment regimens, more than 80% of children with NHL will be cured. The outcome of treatment varies by a number of factors, including clinical stage, histology and genetic studies [7]. However, treatment results of relapses and refractory disease are still dismal [8]. Prognostic factors include age, localization of the disease, chromosomal alterations, tumor burden and response to treatment. The outcome of infants [4] and adolescents [9] is poorer as compared to young children. Patients with limited disease have excellent outcome. Lactate dehydrogenase (LDH) is a surrogate marker for tumor burden, especially in mature B lymphomas where it is used as a stratification factor [10]. Minimal residual disease (MRD) follow-up is of prognostic value in some NHL types. For instance, minimal infiltration of bone marrow and peripheral blood is detected in about 50% of patients with ALCL, using NPM-ALK fusion gene by molecular techniques, showing correlation with clinical stage of the disease [11]. The prognostic factor of the greatest significance is the choice of adequate treatment based on patient's stratification which requires meticulous diagnostic work-up.

MATURE B LYMPHOMAS

Mature B lymphomas are the most common NHL subtype contributing to more than 50% of cases (Table 1). Most of them are classified as Burkitt lymphoma (BL). Other subtypes are less frequent including diffuse large B-cell lymphoma (DLBCL) and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (intermediate DLBCL/BL). Distinguishing between BL and DLBCL in children is not of great significance since they do not require different treatment. The distinction between BL and intermediate DLBCL/BL is of uncertain clinical significance.

BL is usually divided into sporadic or endemic variant, and it is characterized by variable clinical manifestations. Endemic BL is usually seen among patients in Africa. The typical clinical presentation is affection of the jaw or other facial bones. The most frequent clinical manifestation of sporadic BL is diffuse abdominal mass. Elevated LDH which is used as a stratification marker is associated with poor prognosis, especially if elevated more than two to three times of the upper level of normal for age [10]. Morphologically, BL is a diffuse mature B lymphoma presented with monotonous medium sized lymphoid cells, showing high proliferation and apoptosis. The microscopic "starry sky" appearance is due to scattered macrophages containing apoptotic tumor cell bodies.

BL is characterized by the expression of surface immunoglobulin and other antigens of B cell lineage, such as CD 19, CD 20, CD 22 and CD 79a, with a frequent presentation of CD10 [5]. Cytogenetic analysis reveals one of three translocations involving c-myc protooncogene. Detection of one of these translocations is the gold standard for diagnosis. The classical translocation t(8;14)(q24;q32) can be detected in about 85% of cases. This translocation causes fusion of c-myc, which encodes a transcription factor significant for the regulation of cell cycle, with the immunoglobulin heavy chain gene locus. In about 15% of cases, c-myc is fused with the immunoglobulin kappa light chain gene locus [t(2;8)(p11;q24)] or the lambda light chain [t(8;22)(q24;q11)] [12]. Other cytogenetic abnormalities are associated with a poor outcome. They include chromosomes 1q, 7q, or 13q [13].

Patients with localized disease, without CNS or bone marrow infiltration have estimated 5-year event-free survival and 5-year overall survival over 90% [14, 15]. Patients

with an advanced stage disease, especially those with CNS involvement have poorer prognosis. Successful treatment of children with BL is limited regarding research on new therapeutics including recombinant anti-CD20 antibody (rituximab) which is widely used for the treatment of mature CD20+ B cell lymphomas in adults [16]. Rituximab will be considered in future randomized studies in children, especially in patients with advanced disease or relapsed/refractory BL.

DLBCL contribute with about 10% of all childhood NHL (Table 1). DLBCL are a heterogeneous group of lymphomas, and are presented more frequently as a localized disease, rarely involving bone marrow and CNS [6]. Different clinical and biological DLBCL variants probably do not differ in clinical presentation in children.

DLBCL feature morphologically variable blasts of B-lineage with diffuse infiltration of lymph nodes or extranodal sites. Most of them show CD20-positivity. In CD20-negative DLBCL, other B-cell marker expression can be detected, such as CD79a, CD19, Pax5 or immunoglobulin. Immunophenotyping studies of childhood DLBCL are few [17]. Majority of pediatric DLBCL express CD10 and BCL6. BCL2 can be detected in about 40% of patients. Breaks in *BCL2* or *BCL2* to *IGH* fusion by translocation t(14;18) (q32;q21) are practically never seen in childhood DLBCL [17, 18], as well as *BCL6* breaks [18]. However, both BCL2 and BCL6 proteins can frequently be shown by immunohistochemistry analysis. Other genetic abnormalities are also very rare and are limited to single cases only [18].

About one third of pediatric B-NHL, morphologically assessed as DLBCL, could be reclassified using gene profiling as molecular BL. This fact suggests that BL is much more frequent among childhood B-NHL than defined by morphologic evaluation. Again, no difference in treatment outcomes has been observed on BFM (Berlin-Frankfurt-Muenster)-based therapeutic protocols among subgroups defined by genetic reclassification [19], however these findings may be used for more accurate diagnosis.

The WHO classification of 2008 includes provisional borderline categories for cases that are not obviously DLBCL or BL. This category, formerly labeled as Burkitt-like lymphoma, bears new designation: B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (intermediate DLBCL/BL) [20]. Many cases of intermediate DLBCL/BL are diagnosed in adult patients but rarely in children [19]. These patients usually present with generalized lymphadenopathy or disseminated disease, with frequent affection of extranodal sites and frequent bone marrow infiltration [19].

Difference between BL and intermediate DLBCL/BL is subtle, without clear clinical significance. Contrary to BL, cells of intermediate DLBCL/BL show widespread pleomorphism, or sporadic presence of single nucleoli in most cells. The immunophenotype is comparable to BL: CD19, CD20, CD22, CD79a, and germinal center-associated molecules, CD10 and BCL6. BCL2 expression is variable as well as Ki67 labeling index [21].

About one half of intermediate DLBCL/BL exhibit 8q24/MYC translocations, frequently with atypical features: rearrangement with a non-immunoglobulin gene, participating in a complex karyotype, and parallel rearrangements of the BCL2 and BCL6 genes. These findings suggest a "double-hit" or "triple-hit" lymphoma which features a second translocation in addition to frequent ones i.e. t(8;14), t(8;22), or t(2;8). These lymphomas are almost never seen in children as is the case with t(14;18) [22]. Previously mentioned gene expression profiling may be also of value in defining the molecular signature of intermediate DLBCL/BL.

Despite all of the abovementioned data, children with intermediate DLBCL/BL do not have a poor prognosis while the prognosis in young adults is not clear [23]. Treatment regimens used for BL and DLBCL in children yield high cure rates [14].

LYMPHOBLASTIC LYMPHOMAS

Lymphoblastic lymphomas (LBL) consist of immature lymphoid cells. They contribute with approximately 30% of all childhood NHL making them the second most frequent NHL subtype (Table 1). The morphology of the cells cannot be distinguished from the lymphoblasts of precursor cell acute lymphoblastic leukemia (ALL) i.e. terminal deoxynucleotidyl transferase (TdT) positive blasts. LBL are primarily differentiated from ALL based on the extent of bone marrow infiltration by blast cells. In cases with less than 25% bone marrow infiltration, the diagnosis of T-LBL is made while in those with 25% or more, the patients are diagnosed with ALL [2].

Ninety percent of pediatric LBL are T-LBL [6]. WHO classification combines T-LBL and T-ALL into the same, single category of T lymphoblastic leukemia/lymphoma. Whether they are two distinct entities with overlapping characteristics or the same disease, is a subject of ongoing discussion. T-LBL usually presents with an anterior mediastinal mass whereas T-ALL predominantly presents with bone marrow disease causing peripheral blood abnormalities [6]. These two entities might be biologically different as suggested by some slight immunophenotypic, cytogenetic and molecular distinctions [24]. Cure rates for T-LBL are high, nearing 80%, using contemporary chemotherapy regimens for ALL [25, 26, 27]. However, established prognostic markers in T-ALL, such as prednisone response, BM response and MRD evaluation cannot be used in patients with T-LBL [24], and thus a reliable pretreatment stratification of T-LBL patients is not possible. Furthermore, data about useful prognostic markers in T-LBL are limited.

Generally, immunophenotype of T-LBL is similar to T-ALL; TdT positivity and combination of T-cell antigens such as CD2, CD5, and CD7 in most of the cases [28]. Cytoplasmic and/or surface CD3 is positive in nearly all T-LBL cases, while CD4 and CD8 are positive in more than 70%. Contrary to T-ALL, frequent CD4/CD8 double positivity as well as CD1a positivity suggests derivation of T-LBL from a more mature thymocyte stage [29]. Sometimes, aberrant myeloid antigen expression (CD33

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and CD13) is present [30] as well as co-expression of B-cell antigens or stem-cell markers. Small minority of T-LBL does not express TdT. However, these features do not convey inferior outcome in T-LBL [28]. For that reason, immunophenotype is important for diagnosis but not for prognosis in childhood T-LBL.

Chromosomal abnormalities in childhood T-LBL are not clearly defined, however common aberrations seen in T-ALL are also found in T-LBL [29] and they are not used as a stratification tool.

Many oncogenic markers are described in patients with T-ALL/T-LBL, however they are only present in a small number of patients, without clear prognostic value. Loss of heterozygosity (LOH) at chromosome 6q16, mutations of *NOTCH1* as well as F-box and WD40 domain protein 7 (*FBXW7*) mutations show most potential as prognostic markers. LOH at 6q was reported as an unfavorable prognostic marker with an increased risk of relapse among 108 patients with T-LBL, in a recent study [31]. In this study, 19% patients with LOH at chromosome 6 had an associated 5-year cumulative incidence of relapse greater than 60%. Another prognostic marker, *NOTCH1* is a gene encoding a receptor included in the regulation of T-cell development. Its mutation has been reported in more than half of T-ALLs [32]. Alternatively, FBXW7 protein, which plays a critical role in intracellular degradation of *NOTCH1*, is also implicated as a prognostic factor in T-ALL. Mutations in *NOTCH1/FBXW7* were reported as a good prognostic factor in a study of 54 children with T-LBL [33]. More than half of patients in the study bore mutations that conveyed improved event-free survival and overall survival in this subgroup. Similar findings in 64% among 113 patients with T-LBL were published by a NHL-BFM study group, again with favorable prognosis [34]. The ongoing research of the NHL-BFM group will include these alterations into patient stratification. A recent study analyzed LOH6q and *NOTCH1/FBXW7* mutations in 217 children with T-LBL [35]. Twelve percent of patients with LOH6q had a lower event-free survival (EFS) compared to those without this alteration, while 60% of patients with *NOTCH1* mutations had a higher EFS when compared to patients without mutation. Future trials are needed with the aim of decreasing treatment intensity in low risk patients while increasing or introducing new targeted treatment regimens in high-risk patients with T-LBL, defined by the aforementioned newly discovered genetic markers. Another aspect of treatment individualization is represented by the current use of pharmacogenomic markers such as gene polymorphisms important for metabolism of drugs. One of these pharmacogenomic markers is the detection of *TPMT* gene polymorphisms correlating with the metabolism and toxicity of thiopurine drugs [36, 37].

ANAPLASTIC LARGE CELL LYMPHOMAS

ALCL contribute with up to 15% of all pediatric NHL (Table 1). This lymphoma subtype usually manifests aggressively, while extranodal involvement may be present or absent. Characteristic manifestation includes lymphadenopathy with possible involvement of skin or involvement of subcutaneous tissues, with frequent fever and constitutional symptoms [6]. Mediastinal mass and involvement of viscera and skin are recognized as factors of inferior prognosis [38]. Three morphological variants of ALCL are defined in the WHO classification; common variant, with typical large anaplastic cells, lymphohistiocytic variant and small cell variant [2]. The latter two variants convey inferior prognosis [39]. One of the hallmarks of ALCL present in most pediatric cases is the translocation t(2;5)(p23;q35). This translocation produces the fusion of the nucleophosmin gene (NPM) at chromosome 5q35 and anaplastic lymphoma kinase gene (ALK) at 2p23 position. Children and young adults are characteristically affected by the ALK+ ALCL which results in better prognosis as compared to ALK-ALCL [40]. ALK negative form of ALCL is limited only to single case reports or small case series in children. Using anti-ALK antibodies is a golden standard which makes the diagnosis of ALK+ALCL straightforward and readily available [41]. About 10-30% of patients show initial BM involvement on conventional morphology and immunophenotyping. Using molecular genetics seems to be more sensitive, detecting more than half of cases [11]. However, peripheral blood count alterations are usually rare but they are mostly found in children with ALK+ small cell variant [42].

Anaplastic cells showing T/null immunophenotype are typically proliferated in ALCL and they express Ki-1 (CD30) antigen. Cells of this lymphoma subtype usually show CD4 as a T-cell activation marker, although with a loss of pan–T-cell antigens, mostly CD3 as a manifestation of defective T-cell signalling [43]. T-cell origin of this neoplasm may be confirmed by immunostaining for CD43, CD45RO, CD2, CD4, CD5, CD7, and CD8. The latter antigen is positive in only few ALCL. Most ALK+ ALCL reveal clonal rearrangement of T-cell receptor (TCR) gene. The absence of the abovementioned T-cell antigens in otherwise typical ALCL is deemed "null" phenotype [44, 45]. Around 10% of ALCLs show a simultaneous presence of B-cell clone [45]. On the other hand, myeloid antigen expression such as CD13 and CD33 can be detected in a vast majority of ALCLs [46] erroneously suggesting the diagnosis of acute leukemia. The typical anaplastic large cells usually show positivity for epithelial membrane antigen (EMA+) and T-cell intracellular antigen 1 (TIA-1+).

NPM-ALK rearrangement detected by PCR is representative for ALCL and can be used for the diagnosis and confirmation of BM infiltration at submicroscopic level. Different morphological types of ALCL have different gene expression profiles. The genes involved are important for the regulation of cell cycle, cell proliferation, adhesion and migration. Secondary genomic imbalances can be detected in more than half of ALK+ALCLs. A lower number of these secondary aberrations correlate with better survival [47]. However, there are studies which have not confirmed this fact [48].

ALK+ALCL treated with the usual chemotherapy based on regimens for mature B-cell lymphomas, have a good

prognosis with 5-year EFS – up to 75% [7]. Research in proteomics recognized alterations in proteins included ALK signaling pathway [49], however without clear pathogenetic role. If proven significant, they may become targets for novel therapeutic agents. Available novel therapies are being tested in randomized trials and include small-molecule inhibitor of the receptor tyrosine kinases, crizotinib and antibody-drug conjugate against CD30, brentuximab vedotin [50]. Additionally, immune therapy with anti-ALK vaccine may also become reality since ALK is not normally expressed in human cells, except for central nervous system. ALK is known to be immunogenic since most patients with ALK+ALCL have detectable anti-ALK antibodies [51].

CONCLUSION

Pediatric non-Hodgkin lymphomas are very heterogeneous in terms of morphology, immunophenotype, genetic alterations, therapy response and risk of relapse. Excellent improvement in treatment results has been achieved thanks to understanding of these characteristics. On the other hand, the relapsed or refractory disease conveys much poorer prognosis. This fact requires much better stratification based on still undefined prognostic markers which would ideally recognize distinct groups of patients requiring different therapeutic regimens. In this setting, selected patients may be offered less toxic regimens while more aggressive treatment or novel targeted therapeutics could be reserved for patients with poor prognostic parameters and for those who do not respond to conventional treatment. These two groups of pediatric patients with NHL cannot be readily distinguished by prognostic markers used nowadays. Defining novel diagnostic and prognostic markers should improve diagnosis and prognosis as well as patient follow-up. It should also allow introduction of individually tailored treatment regimens in selected groups of patients with NHL, with the main goal of improving treatment results and decreasing short- and long-term complications.

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Нехочкински лимфоми код деце: можемо ли боље?

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КРАТАК САДРЖАЈ

Педијатријски нехочкински лимфоми су разнородна група малигнитета с различитим клиничким, патолошким, имунофенотипским и генетским особинама. Већина нехочкинских лимфома дечјег доба се може класификовати у једну од три главне хистолошке категорије: зреле Б-неоплазме, лимфобластне лимфоме и крупноћелијске анапластичне лимфоме. Савременим терапијским приступом се постиже излечење код више од 80% болесника. С друге стране, болест која не одговори на терапију и рецидиви имају лошу прогнозу. Стога је неопходно боље разврставање болесника засновано на прогностичким маркерима, који би идеално требало да раздвоје различите групе болесника којима је потребна другачија терапија. Дефинисање нових дијагностичких и прогностичких маркера би требало да побољша дијагнозу, прогнозу, праћење болести и увођење индивидуализованог терапијског приступа код одабраних болесника, ради побољшања резултата лечења и смањења непосредних и позних последица лечења.

Кључне речи: нехочкински лимфом; деца; класификација; дијагноза; прогноза; терапија

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