

Non-Hodgkin's Lymphoma of Childhood

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Introduction

Malignant lymphomas which comprise Hodgkin's disease and non-Hodgkin's lymphoma (NHL), are the third most common malignancy among children and adolescents.¹⁻⁵ Among children less than 15 years of age, NHL is more frequent; however, in patients up to 18 years of age, Hodgkin's disease is predominant.^{6,7,8}

The incidence of NHL increases steadily throughout life, in contrast to Hodgkin's disease, which has a bimodal age distribution with peaks in early and late adulthood.² Children at risk include those with acquired immunodeficiency syndrome, those with congenital immunodeficiency syndromes (ataxia-telangiectasia, Wiskott-Aldrich syndrome, or X-linked lymphoproliferative syndrome), and those who have received immunosuppressive therapy (e.g., recipients of bone marrow or organ transplants).^{2,9,10,11,12} Deficient T-cell function may contribute in part to this increased risk.

There are differences in both the incidence and proportion of histologic subtypes in different parts of the world.^{1,2} For example, the NHLs are very rare in Japan, while they account for approximately half of all childhood malignancies in equatorial Africa. Burkitt's lymphoma is the predominant histologic subtype in equatorial Africa (endemic Burkitt's lymphoma) and northeast Brazil,¹³ but comprises approximately one-third of cases in the United States and western Europe. There is a significant association between Epstein-Barr virus (EBV) and endemic Burkitt's lymphoma.² Although no direct pathogenic role has been dem-

onstrated for this virus, it has been speculated that as a B-cell mitogen, EBV increases the target pool of cells for transformation. A recently identified EBV nuclear antigen 1 (EBNA-1) variant has been found associated with the majority of Burkitt's lymphoma cases, suggesting that this mutation may provide a growth advantage to lymphoma cells by modifying EBNA-1 function in some way.¹⁴ EBV is associated with 90% of African (endemic) Burkitt's lymphoma cases, but with only 15% of cases in the United States (sporadic).^{15,16,17}

Classification

The National Cancer Institute (NCI) Working Formulation, divides the tumors into three grades: low, intermediate, and high.⁷ In contrast to the NHLs in adults, which are primarily low and intermediate grade, the NHLs in children are predominantly diffuse high-grade tumors, which comprise the small noncleaved cell, lymphoblastic, and large cell subtypes (see **Table 1**).

Small noncleaved cell

Burkitt lymphoma is a diffuse B-cell lymphoma expressing surface immunoglobulin (usually IgM) as well as other B cell-associated antigens, including CD19 and CD20.^{2,18} These lymphomas contain sheets of monomorphic lymphoid cells with basophilic cytoplasm and one or more prominent nucleoli. The "starry sky" appearance frequently associated with this tumor is caused by tingible body macrophages in

Table 1. Clinical and Biologic Characteristics of Non-Hodgkin's Lymphoma in Children⁶⁶

Subtype*	Proportion of Cases (%)†	Phenotype	Primary Site	Translocation	Affected Genes‡
Small noncleaved cell (Burkitt's)	39	B cell	Abdomen or head and neck	t(8;14)(q24;q32) t(2;8)(p11;q24) t(8;22)(q24;q11)	IgH - c-MYC Igκ - c-MYC Igλ - c-MYC
Lymphoblastic	28	T-cell§	Mediastinum or head and neck	t(1;14)(p32;q11) t(11;14)(p13;q11) t(11;14)(p15;q11) t(10;14)(q24;q11) t(7;19)(q35;p13) t(8;14)(q24;q11) t(1;7)(p34;q34)	TCRαδ - TAL1 TCRαδ - RHOMB2 TCRαδ - RHOMB1 TCRαδ - HOX11 TCRβ - LYL1 TCRαδ - MYC TCRβ - LCK
Large cell	26	B cell, T cell, indeterminate	Mediastinum, abdomen, head and neck, or skin	t(2;5)(p23;q35)	NPM-ALK

* The subtypes are classified according to the National Cancer Institute's working formulation.

† Proportion at St. Jude Children's Research Hospital; other histotypes account for approximately 7%.

‡ Ig denotes immunoglobulin and TCR T-cell receptor.

§ B-cell-progenitor variants have also been described.

the field.

Cytogenetically, Burkitt lymphomas are characterized by the presence of one of three reciprocal chromosomal translocations, resulting in the juxtaposition of the *c-myc* proto-oncogene on chromosome 8 with one of the three immunoglobulin genes, resulting in deregulation of the *c-myc* gene.^{2,19,20,21} The classical translocation $t(8;14)(q24;q32)$, involving the heavy chain immunoglobulin locus, is identified in approximately 85% of cases. Each of two variant translocations, $t(2;8)(p11;q24)$ and $t(8;22)(q24;q11)$, involving one of the two light chain immunoglobulin loci are identified in the remaining cases.

Expression of the *c-myc* gene is associated with cell proliferation. The *c-myc* protein forms heterodimers with related proteins (e.g., MAX, MAD) that subsequently influence cell cycling.²²⁻²⁶ In Burkitt's lymphoma, deregulated expression of *c-myc* may result in an increased proportion of MYC-MAX complexes, leading to tumor cell proliferation.²⁷

There are various theories about the pathogenic mechanism of *c-myc* deregulation in Burkitt's lymphoma.²⁸⁻³¹ The invariable presence of mutations (truncations or point mutations) in the translocated *c-myc* gene has led to speculation that these mutations result in deregulated expression. Other hypotheses focus on *c-myc*'s juxtaposition to the immunoglobulin loci—some suggesting that the immunoglobulin gene usurps control over the translocated *c-myc* gene, perhaps through long-range enhancer sequences.^{28,30}

The apparent abrogation of *c-myc*'s induction of apoptosis suggests that other factors besides deregulation of *c-myc* are involved in the pathogenesis of Burkitt's lymphoma.³²⁻³⁴ The identity and potential role in pathogenesis of other oncogenes or tumor suppressor genes is currently under investigation.^{32,35} Abnormalities in the *p53* gene have been identified in cases of SNCC NHL and B-cell ALL,³⁶⁻³⁸ which differ from those seen in solid tumors such as lung, breast, and colorectal carcinomas. The frequency of mutations in primary tumor biopsies is much lower than that reported in cell lines, which are usually established from cells obtained at relapse (33% vs 70%, respectively), suggesting that *p53* mutations in Burkitt's lymphomas may be involved in disease progression.³⁷

Lymphoblastic lymphoma

The morphology of these tumor cells is similar to that of acute lymphoblastic leukemia. The majority (>95%) are of T-cell immunophenotype; however, a small percentage have a B-cell progenitor immunophenotype and are associated with cutaneous involvement.³⁹⁻⁴²

It is generally assumed that lymphoblastic lymphoma and T-cell leukemia are different presentations of the same disease process; however this has yet to be proved.⁴³ The reciprocal chromosomal translocations identified in T-cell leukemia and lymphoblastic lymphoma typically involve one of the T-cell receptor genes and result in deregulation of the reciprocal partner gene (e.g., *TAL1*, *HOX11*, and *RHOMB* genes).⁴⁴⁻⁵²

Large cell lymphoma

The large cell lymphomas are a heterogeneous group of malignancies that vary in histology and immunophenotype (T-cell, B-cell, or non-B, non-T cell).⁵³⁻⁵⁵ Approximately 50% of cases may be classified as having anaplastic features (abundant cytoplasm, atypical lobulated nuclei, and prominent nucleoli in sheets of adherent cells with sinusoidal involvement).⁵⁴⁻⁵⁷ These anaplastic large cell lymphomas appear to represent a unique clinicopathologic entity and are associated with CD30 expression (an activation antigen first identified on Reed-Sternberg cells),⁵⁸ the presence of the $t(2;5)(p23;q35)$ translocation,^{55,57,59,60,61} a T-cell or non-T, non-B cell immunophenotype, and extranodal disease sites (e.g., skin, bone, and soft tissue).

The $t(2;5)$ chromosomal abnormality is present in approximately 50% of cases of pediatric large cell NHL.⁶⁰ It results in fusion of the involved genes (the amino-terminal portion of the nucleophosmin gene, *NPM*, on chromosome 5 with the catalytic domain of the anaplastic lymphoma kinase gene, *ALK*, on chromosome 2) on the *der(5)* chromosome.^{62,63} The molecular characterization of the $t(2;5)$ has led to the development of a reverse-transcriptase polymerase chain-reaction (RT-PCR) assay that enables the detection of *NPM-ALK* transcripts, even in patients with no detectable $t(2;5)$ by standard cytogenetics.⁶⁴

Clinical Features

The clinical features at presentation vary with both primary site and extent of disease spread.^{2,9,39,65,66,68} Children who have a mediastinal mass may present with a spectrum of symptoms ranging from cough to severe respiratory distress caused by direct airway compression. Primary involvement of the abdomen may be associated with nausea, vomiting, and abdominal pain. Involvement of the bone marrow may result in pancytopenia with associated pallor and bruising. Involvement of the central nervous system (CNS) may be associated with cranial nerve palsies and/or symptoms of increased intracranial pressure such as headache and vision changes. Cutaneous involvement may also occur, and is usually associated with CD30+ anaplastic large cell lymphoma.^{55,61} Bone involvement may be associated with pain or limping.

Diagnosis

The diagnosis of NHL is usually established by examination of tissue obtained by open biopsy of the involved site. Sufficient tissue should be obtained not only for histology, but also for immunophenotypic, cytogenetic, and molecular studies. In children with suspected NHL, a bone marrow and cerebrospinal fluid (CSF) examination may be diagnostic, averting the need for more invasive procedures and possible increased morbidity.

Initial laboratory evaluation should include a complete blood count with differential, a chemistry profile (electrolytes, BUN, creatinine, LDH, calcium, phosphorus, and uric acid) and an HIV screen.

Staging

It is imperative that a meticulous staging workup be performed, because therapy is determined in part by location and degree of disease spread. Because NHL in children grows very rapidly, there should be no unnecessary delay in the staging workup or in starting appropriate therapy. Diagnostic imaging studies should include CT scanning of chest, abdomen, and pelvis and bone scanning. Gallium scanning may also be helpful in selected cases, particularly in following residual masses that were gallium- positive at diagnosis. The cerebrospinal fluid and bone marrow must be examined in all patients. Bilateral posterior iliac crest aspiration and biopsy increases the chance of identifying marrow involvement, thus reducing the possibility of understimating the disease stage.⁶⁹ Upon completion of the workup, the stage of disease is usually determined according to the St. Jude Staging System described by Murphy (**Table 2**).⁷⁰

Table 2. Stages of Non-Hodgkin's Lymphoma*

Stage I

A single tumor (extranodal) or involvement of a single anatomical area (nodal), with the exclusion of the mediastinum and abdomen.

Stage II

A single tumor (extranodal) with regional node involvement.

Two or more nodal areas on the same side of the diaphragm.

Two single (extranodal) tumors, with or without regional node involvement on the same side of the diaphragm.

A primary gastrointestinal tract tumor (usually in the ileocecal area), with or without involvement of associated mesenteric nodes, that is completely resectable.

Stage III

Two single tumors (extranodal) on opposite sides of the diaphragm.

Two or more nodal areas above and below the diaphragm.

Any primary intrathoracic tumor (mediastinal, pleural, or thymic).

Extensive primary intraabdominal disease.

Any paraspinal or epidural tumor, whether or not other sites are involved.

Stage IV

Any of the above findings with initial involvement of the central nervous system, bone marrow, or both.

*Based on the classification proposed by Murphy.⁷⁰

Therapy

General principles

The dramatic improvement in treatment outcome achieved over the past 25 years is in large part due to the refinement in multiagent chemotherapeutic strategies through sequential clinical trials.^{2,9,53,71-108} Current strategies feature a stage, histology- and immunophenotype-directed treatment approach. There is a minimal role for radiation therapy and surgery in the management of childhood NHL.^{2,9}

To prevent the spread of disease to the CNS, prophylactic intrathecal (IT) and high-dose systemic chemotherapy are used in most children. Some groups have included cranial radiation for CNS prophylaxis in pediatric lymphoblastic lymphoma; however, this approach is controversial.¹⁰¹ Among children who present with overt CNS disease, intensification of both intrathecal and systemic chemotherapy is often needed, and, with the exception of Burkitt's lymphoma, the addition of cranial irradiation.

Limited stage disease

The excellent prognosis for children with limited stage disease has prompted investigators to develop treatment strategies that reduce treatment-related morbidity while maintaining an excellent treatment result (**Table 3**).^{71,73,74,95,96} For example, in the first of two sequential trials performed by the Pediatric Oncology Group,⁷⁴ it was demonstrated that involved field radiation therapy could be safely deleted from a 33-week chemotherapy regimen that comprised 3 courses of CHOP (cyclophosphamide, Adriamycin, vincristine and prednisone) given over a 9-week period, followed by a 24-week maintenance phase consisting of weekly 6-mercaptopurine and methotrexate. In the subsequent trial, they demonstrated that the 24-week maintenance phase could be deleted without compromising the treatment result for those with either large cell or small noncleaved NHL.

Advanced stage disease

In the United States, efforts to improve the treatment outcome for children with advanced stage disease have primarily examined strategies to increase treatment intensity in

Table 3: Treatment Outcome for Limited -Stage NHL

Regimen	Strategy	No. of Patients	Outcome
SJCRH ⁷³	Decrease intensity	28	86% 2 yr DFS
CCG ^{96*}	Shorten duration	54	98% 2 yr EFS
POG ⁷⁴	Delete radiation	131	86% 5 yr CCR
	Delete continuation	113	89% 5 yr CCR
SFOP ^{71*}	Surgical resection	44	96% 3 yr EFS

* Excludes lymphoblastic NHL

DFS: disease-free survival; EFS: event-free survival; CCR: continuous complete remission

Table 4: Treatment Outcome for Advanced Stage Small Noncleaved Cell Non-Hodgkin's Lymphoma

Protocol	Stage	No. Patients	Event-Free Survival	Reference
Total B	III IV/B-ALL	17 4/8	2 yr EFS = 81% 2 yr EFS = 17%	72
POG 8617	IV B-ALL	34 47	4 yr EFS = 79 %x 9% 4 yr EFS = 65 %x 8%	76
LMB 84*	III IV/B-ALL (CNS-)	167 34	2 yr EFS = 80% (SE 3) 2 yr EFS = 68% (SE 8)	77
LMB 86*	B-ALL (CNS-) B-ALL (CNS+)	11 24	>1 yr EFS = 82% (SD 12) >1 yr EFS = 75% (SD 9)	78
LMB 89*	III IV/ALL	279 165	3 yr EFS = 93% %x 3% 3 yr EFS = 88% %x 4%	71
BFM 81	B-ALL	22	5 yr EFS = 40% (SD 6%)	79
BFM 83	B-ALL	24	5 yr EFS = 50% (SD 10%)	79
BFM 86	B-ALL	41	5 yr EFS = 78% (SD 6%)	79
BFM 90	III IV B-ALL	171 23 56	6 yr EFS = 86% (SD 8%) 6 yr EFS = 83% (SD 3%) 6 yr EFS = 76% (SD 8%)	102
CCG LSA ₂ L ₂ vs. COMP	III/IV/B-ALL III/IV/B-ALL	44 93	5 yr EFS = 29% (95% CI 16-43%) 5 yr EFS = 50% (95% CI 39-60%)	80
CCG COMP vs. D-comp (randomized)	III/IV/B-ALL	175	2 yr EFS = 65%	81
CCG* Orange vs. LMB 86	III/IV/B-ALL III/IV/B-ALL	43 42	12 mo EFS = 83% 12 mo EFS = 84%	82 82
NCI* 77-04	III IV	30 9	3 yr EFS = 57% %x 9% 3 yr EFS = 13% %x 12%	83
CODOX/VIPA	III/IV/B-ALL	75	1 yr EFS = 89%	105
Boston HiC-COM	III IV/B-ALL	12 8	2 yr EFS = 95% (CI 54% - 99%) 2 yr EFS = 50% (CI 15% - 78%)	84

* Includes patients with B-cell large cell NHL

the framework of a histology directed approach,^{53,54,72,75,76,80-85,87-93,98} whereas in Europe, an immunophenotype-directed strategy is usually employed.^{71,77-79,86,94,95,97,101-103,106-108} Advances in the treatment outcome of patients with SNCC NHL (Table 4) were initially made by including high-dose methotrexate and/or cytarabine^{72,75-77,79,83} even in regimens given over as short a period as 2-4 months.^{77,84} More recently, further improvement has been achieved by dose-intensification of therapy and by the inclusion of additional active agents such as etoposide and/or ifosfamide.^{71,78,79,82,101,104} Most of the regimens used successfully to treat lymphoblastic NHL are similar to or derived from those designed

for children with high risk T-cell acute lymphoblastic leukemia (Table 5).^{80,85,87-89,95,99,100} The optimal approach to the treatment of advanced stage large cell NHL has been a challenge to identify, both because of the biologic heterogeneity of these tumors and the markedly varied treatment strategies reported. In the United States, children with large cell NHL are treated on histology-directed protocols (Table 6).^{53,54,80,81,90,91,98} Most of these histology-directed strategies are CHOP-based (cyclophosphamide, Adriamycin, vincristine, and prednisone), with current trials examining the benefit of adding agents such as carboplatin, high-dose cytarabine, etoposide, ifosfamide, and high-dose methotrexate.

Table 5: Treatment Outcome for Advanced Stage Lymphoblastic Non-Hodgkin's Lymphoma

Protocol	Stage	No. Patients	Event-free Survival	Reference
LSA ₂ L ₂ (modified) POG 7615	III	24	3 yr EFS = 57%	85
LSA ₂ L ₂ (modified) CCG-551	III/IV	124	5 yr EFS = 64%	80
BFM 75/81	III/IV	42	4 yr EFS = 78%	86
BFM 86/90	III IV	119 30	pEFS* = 87% (SE 3%) pEFS* = 90% (SE 6%)	106
X-H SJCRH	III/IV	22	4 yr DFS = 73%	87
APO (Dana Farber)	III/IV	21	3 yr DFS = 58% ^{sx} 23%	88
77-04 (NCI)	III	10	4 yr EFS = 70%	83
A-COP + (POG)	III	33	3 yr DFS = 54% ^{sx} 9%	89

*Median observation time = 4.3 years.

Table 6: Treatment Outcome for Advanced Stage Large Cell non-Hodgkin's Lymphoma

Protocol	Stage	No. Patients	Event-free Survival	Reference
COMP	III & IV	42	5 Yr EFS = 52%	80
LSA ₂ L ₂	III & IV	18	5 yr EFS = 43%	80
APO	III & IV	—	3 yr EFS = ~65%	90
ACOP +	III & IV	22	4 yr EFS = 67%	91
COMP vs. D-COMP	III	86	2 yr EFS = 66%	81
CHOP	III & IV	21	3 yr EFS 62% ^{sx} 11%	53
MACOP-B	III & IV	11	3 yr EFS 55% ^{sx} 16%	92

European trials^{71,101} for children with large cell NHL have generally been designed according to immunophenotype; children with B-cell tumors are treated like those with SNCC NHL,^{107,108} those with T-cell tumors are treated like those with lymphoblastic lymphoma or T-ALL; and those with CD30-positive anaplastic lymphomas are treated with various approaches, including therapy designed for Burkitt's lymphoma.⁹⁴

Salvage

The prognosis is generally considered to be poor for children who fail initial therapy, particularly if they have received intensive therapy up front. Current approaches to the management of these patients incorporate intensive multiagent therapy, which may be followed by hematopoietic stem cell or bone marrow transplantation. Various multiagent regimens have been studied, including VIPA¹¹⁰ (etoposide, ifosfamide, and cytarabine), DHAP⁹² (dexamethasone, cytarabine, and cisplatin), ICE¹¹¹ (ifosfamide, carboplatin, and etoposide), and MIED (methotrexate, ifosfamide, etoposide, and dexamethasone). Children who are shown to have chemosensitive recurrent disease are considered candidates for an intensification phase with autologous hematopoietic stem cell support or allogeneic bone marrow transplantation.¹¹²⁻¹¹⁵

Future Directions

Approximately 30% of children with NHL either relapse or don't respond to initial therapy.⁶ Late effects also remain a concern.^{120,121} Thus, a major goal for the future is to develop treatment strategies that will provide a cure for the remaining 30% while reducing treatment-related morbidity. The identification of both clinical and biologic features that predict treatment outcome may enable investigators to determine which patients need novel or aggressive therapy.^{122,123} The continued investigation of lymphoma related cytogenetic and molecular abnormalities may lead to novel and more successful treatment strategies, including those directed toward tumor-specific molecular lesions.

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