Non-Hodgkin Lymphomas in Children

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Introduction

Non-Hodgkin lymphomas, clonal disorders of the immune system, are caused by the transformation of lymphoid progenitor cells at a particular stage of differentiation.

The significant variations in the clinical and biological characteristics of lymphoid malignancies among young patients reflect the fact that the lymphoid system is functionally diverse, has a wide anatomic distribution, interacts with other cellular systems, and undergoes continuous remodeling during childhood and adolescence.

NHL is classified according to the lymphoid lineage involved. B-lineage NHL (Burkitt, lymphoblastic, and large B-cell lymphomas) represents about 50% of cases; T-lineage accounts for the remaining half (lymphoblastic and anaplastic large-cell lymphomas).

Epidemiology and Risk Factors

In the U.S., 800 (6.5%) of the 12,400 new cases of cancer diagnosed annually in children, adolescents, and adults younger than 20 years are NHL.¹ NHL represents 3% of all cases of pediatric cancer affecting children younger than 5 years of age and 9% of the cases of those 15 to 19 years of age (Figure 1).
During the past 20 years, the incidence of NHL appears to have increased in the U.S. While the incidence of NHL in children younger than 15 years remained stable from 1975 through 1995, that of adolescents increased for unknown reasons from 10.7 per million (1975-1979) to 16.3 per million (1990-1995). The incidence of NHL is higher among boys, and the rate of NHL in all age groups is markedly higher for white American children than for black American children.

International variation in the incidence of NHL has been reported being Burkitt’s lymphoma more common in tropical areas such as Equadorial Africa.
In this part of the world, endemic Burkitt’s lymphoma usually affects the jaw and it’s geographical distribution is similar to malaria.

The incidence of pediatric NHL is likely to be affected by the environment since the disease typically originates in immune-system structures that come in contact with the environment, such as the Peyer follicles in the bowel and the lymphoid nodules at airway branch points. Such a relation has already been observed between Epstein-Barr virus (EBV) infection (with malaria as a co-factor) and the incidence of Burkitt lymphoma. Moreover, AIDS (acquired immunodeficiency syndrome), which is cause by human immunodeficiency virus (HIV) infection, has been associated with an increased risk of NHL. However, in developing countries, the lack of population registries makes estimation of this incidence very difficult.

Causes of childhood lymphoid malignancies are largely unknown; and most children with NHL do not appear to have predisposing factors. However, certain factors and specific constitutional syndromes have been associated with an increased predisposition to lymphoid malignancies. For example, increased risk of NHL has been associated with congenital immunodeficiencies such as Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome, and severe combined immunodeficiency.

**Diagnosis and Classification**

A definitive diagnosis of NHL requires examination of the tumor mass (nodal or extranodal). When NHL is suspected, it is best to sample the most accessible, representative nodal or extranodal tumor. When patients have a large mediastinal mass and they are at very high risk of complications during anesthesia, pleural effusion can provide an adequate number of tumor cells for diagnosis. Alternatively, fine needle aspiration of regional lymph nodes, which can be performed without general anesthesia, may also yield adequate material for diagnosis of primary mediastinal lymphoblastic NHL.
However, in most cases, a biopsy procedure is needed to yield sufficient material for an accurate diagnosis.

Cytologic diagnosis of pediatric lymphoma is justified only in emergency cases, and results should be confirmed by immunophenotyping. Although the classification of NHL in general is very complex and the process is still evolving, the classification of pediatric NHL is considered to be simpler than that of its adult counterpart.

Virtually all childhood NHL can be classified into one of three types: Burkitt, lymphoblastic, and large-cell. Each type exhibits diffuse histologic characteristics. In a study of 1,336 children and adolescents, histologic examination indicated that only 17 cases (1.3%) were follicular (nodular) NHL. Rarely, other subtypes of NHL are seen in children, and many can cause a diagnostic dilemma (see session on uncommon forms of pediatric NHL).

Burkitt lymphoma is characterized by sheets of monomorphic lymphoid cells. Commonly, macrophages dispersed throughout the tumor give it the classic “starry sky” appearance. In the bone marrow or blood, the Burkitt cells (in FAB L3 subtype ALL, Figure 2) are relatively uniform in shape, and have a moderate amount of deeply basophilic cytoplasm containing sharply defined, clear vacuoles, and round nuclei containing coarsely reticular chromatin. The cells express monotypic surface immunoglobulin (either IgM k or l light chains) and harbor specific chromosomal translocations involving the C-MYC oncogene. The most common of these cytogenetic abnormalities, present in 80% of cases, is the t(8;14)(q24;q32) translocation. In the remaining cases, t(2;8)(p12;q24) and t(8;22)(q24;q11) translocations are observed.

Lymphoblastic NHL arises from transformed, immature T or B cells. Lymphoblastic NHL that arises from T cells, which accounts for more than 80% of all cases of the disease, expresses an immunophenotypic profile similar to that of normal thymocytes at an intermediate or late stage of differentiation. As with Burkitt NHL, T-cell malignancy is characterized by several cytogenetic abnormalities that cause activation of transcription factors due to specific
translocations in the T-cell receptor genes. Typically, these translocations are juxtaposed with a small number of developmentally important transcription factor genes, including *HOX11 (TLX1), TAL1 (SCL), TAL2, LYL1, BHLHB1, LMO1,* and *LMO2.*

**Figure 2:** FAB L3 cells showing basophilic cytoplasm containing sharply defined, clear vacuoles (May-Grunwald-Giemsa staining X 100)

Large-cell NHL is the most heterogeneous pediatric NHL subtype. Immunophenotypic analysis of large-cell NHL shows that the neoplastic cells can be of T-cell or B-cell lineage or have no lineage-specific markers (null cells). Regardless of the immunophenotype, approximately 40% of large-cell NHL cases express the CD30 (Ki-1) antigen. According to the classification system adopted by the World Health Organization, most pediatric large-cell lymphomas can be classified as diffuse B-cell or anaplastic large-cell lymphoma (ALCL).
Classification as ALCL requires the co-expression of CD30 and the membrane epithelial antigen in lymphoma cells expressing T-cell or null-cell markers.\textsuperscript{9} Approximately 80\% of ALCL cases identified on the basis of this criterion harbor the t(2;5)(p23;q35) chromosomal rearrangement.\textsuperscript{14} This translocation juxtaposes the gene encoding anaplastic lymphoma kinase (ALK) with regulatory elements of the gene encoding nucleophosmin (NPM), a nonribosomal nucleolar phosphoprotein.\textsuperscript{15} Rarely, the ALK gene is involved in other translocations, including t(1;2), t(2;3), inv(2), and t(2;22). Importantly, ALK protein expression can be detected by immunohistochemical study. The use of polyclonal and monoclonal antibodies to detect these proteins aids in diagnosis. Children with ALK-positive ALCL appear to have a better prognosis than do those with other forms of large cell NHL.

**Clinical Manifestations**

Childhood NHL manifests in extremely diverse ways. The dominant clinical manifestations depend on the tumor’s location and the extent of the disease. Virtually any lymphoid tissue can be affected, including peripheral lymph nodes, tonsils, thymus, spleen, and intestinal lymphoid aggregates (Peyer’s patches). In addition, pediatric NHL commonly extends to the bone marrow, CNS, bone, and skin. Since this is a rapidly growing malignancy, these patients present with complaints lasting for only a few days or weeks.

Painless enlargement of the cervical lymph nodes is the most common clinical presentation. In a retrospective chart review conducted at St. Jude Children’s Research Hospital\textsuperscript{16}, one-third of children with NHL had palpable lymph nodes in the head and neck region. Another third presented with primary mediastinum involvement, which is commonly associated with supraclavicular and axillary adenopathy (**Figure 3**).
Figure 3: Mediastinal involvement by lymphoblastic lymphoma

The clinical presentation of patients with a large mediastinal mass is described above. Abdominal presentation of childhood NHL is associated with a rapidly enlarging palpable mass. Tumors in the gastrointestinal tract usually affect the distal ileum, cecum, and mesenteric nodes (Figure 4).
Figure 4: Massive intraperitoneal invasion by Burkitt lymphoma.

Retroperitoneal and renal extension is also common.

Figure 5

Patients with a large abdominal mass complain of intermittent pain in the periumbilical region or right iliac fossa. Nausea, vomiting, and weight loss are also common features. Occasionally, signs of an acute abdomen due to intussusception are the dominant feature. Generally, the primary tumor site is associated with a particular histologic subtype. In patients with Burkitt NHL, an abdominal mass is most common; in lymphoblastic or diffuse, large B-cell NHL,
mediastinal and peripheral lymph node tumors are most common; in ALCL, skin, bone, and soft tissue tumors are most common. When disease is disseminated, it is often impossible to determine the tumor’s primary site. Less-common presentations of NHL include subcutaneous lesions, thyroid and parotid enlargement, proptosis, and spinal cord compression. Although rare, spinal cord compression should be considered a medical emergency, and it should be treated urgently to prevent permanent neurologic deficits. The histologic, immunophenotypic, and cytogenetic characteristics of childhood NHL are listed in Table 1.

<table>
<thead>
<tr>
<th>Histologic type</th>
<th>Immunophenotype</th>
<th>Cytogenetic abnormality</th>
<th>Fusion gene</th>
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<tbody>
<tr>
<td>Burkitt B-cell (mature)</td>
<td>t(8;14)(q24;q32)</td>
<td>MYC-IgH</td>
<td></td>
</tr>
<tr>
<td>Lymphoblastic T-cell</td>
<td>Same as T-cell ALL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-B-cell</td>
<td>Same as pre-B-cell ALL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-cell B-cell</td>
<td>t(2;5)(p23;q32)</td>
<td>NPM-ALK</td>
<td></td>
</tr>
<tr>
<td>Anaplastic large-cell T-cell, null</td>
<td>t(1;2)(q21;p23)</td>
<td>TPM3-ALK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(2;3)(p23;q21)</td>
<td>TFG-ALK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inv(2)(p23q35)</td>
<td>ATIC-ALK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(2;22)(p23;q11)</td>
<td>CTCL-ALK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(X;2)(q11;p23)</td>
<td>MOESIN-ALK</td>
<td></td>
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<tr>
<td></td>
<td>t(2;19)(p23;13)</td>
<td>TPM4-ALK</td>
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*World Health Organization classification*
Laboratory Findings

In patients with NHL, blood counts are usually normal. In those with bone marrow involvement, anemia and thrombocytopenia are common, and circulating lymphomatous cells may be present. As in patients with ALL, serum concentrations of uric acid and lactate dehydrogenase activity (LDH) can be elevated. Although CNS involvement is rare at presentation of NHL, particularly in those with large-cell lymphoma, all patients should undergo lumbar puncture and CSF examination. A prompt radiologic investigation is required to demonstrate areas of tumor involvement and is used to monitor the tumor’s response to therapy.

Whole-body computed tomography (CT) is the imaging modality of choice to determine tumor extent, and radionuclide scanning of all patients with both technetium-99 and gallium-67 is generally performed. The roles of magnetic resonance imaging, photon emission CT, and thallium scanning in childhood NHL have not yet been defined. However, in the initial evaluation, bilateral bone marrow examination is mandatory. Occasionally bone marrow involvement is unilateral. Bone marrow biopsy may reveal tumor involvement that is not clear from examination of the bone marrow aspirate; therefore, to determine disease stage, most investigators recommend bone marrow biopsy as part of the work-up. However, children with massive mediastinal involvement may not tolerate the anesthetic procedure needed to perform bilateral bone marrow aspirations, and biopsies and a single aspirate may be sufficient. Suspected cases of pediatric lymphoma should be diagnosed promptly, and treatment should begin without delay.
Differential Diagnosis

Because of its varied clinical and laboratory manifestations, childhood NHL can mimic several nonmalignant and malignant diseases. Differentiating between a reactive lymphoproliferative process and NHL is rarely difficult. However, diagnosis of NHL is occasionally delayed in patients with localized, painless adenopathy when results of histologic studies of the lymph nodes are inconclusive for the presence of malignancy. Patients with persistent, painless enlargement of the lymph nodes after a 10- to 14-day trial of antibiotic therapy should undergo a lymph node biopsy, preferably surgically, to provide adequate tissue for immunophenotyping and for molecular and conventional studies.

Persistently enlarged lymph nodes in patients with acquired or congenital immunodeficiency represent a substantial diagnostic dilemma. Collectively, these abnormalities have been classified as lymphoproliferative disorders, and they range from reactive polyclonal hyperplasia to true monoclonal malignant lymphomas. Children presenting with an isolated mediastinal mass present a diagnostic challenge because a mediastinal mass can be present at diagnosis of several malignant and nonmalignant conditions, including histoplasmosis, sarcoidosis, Hodgkin disease, germ cell tumor, thymic carcinoma, neuroblastoma, and myeloblastoma. Results of serologic studies can provide evidence of some of these diseases, but a CT-guided needle biopsy procedure is usually necessary to provide tissue for diagnosis.

Primary lymphoma of the bone is commonly misdiagnosed. Indeed, in one St. Jude study, 10 of the 11 patients with biopsy-confirmed primary lymphoma of the bone had previously received an alternative initial diagnosis. To differentiate between primary lymphoma of the bone and other small blue cell tumors, immunohistochemical studies with an extensive panel of markers are required to supplement histologic studies.
**Table 1: Immunophenotypic features of the most common pediatric lymphoma subtypes.**

<table>
<thead>
<tr>
<th>Lymphoma Subtype</th>
<th>T-cell markers</th>
<th>B-cell markers</th>
<th>Other markers</th>
</tr>
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<tbody>
<tr>
<td>T-lymphoblastic lymphoma</td>
<td>Usually positive: CD3 (cytoplasmic), CD5, CD7&lt;br&gt;Occasionally positive: CD4, CD8, CD1a, CD3 (surface)</td>
<td>Occasionally positive: CD10&lt;br&gt;Occasionally positive: CD10</td>
<td>TdT</td>
</tr>
<tr>
<td>B-cell precursor lymphoblastic lymphoma</td>
<td>Usually negative</td>
<td>Usually positive: CD19, CD20, CD79a, CD10&lt;br&gt;Usually negative: sIg</td>
<td>TdT</td>
</tr>
<tr>
<td>Burkitt's lymphoma</td>
<td>Usually negative</td>
<td>Usually positive: sIg, CD20, CD19, CD79a</td>
<td>TdT: Negative</td>
</tr>
<tr>
<td>Diffuse large cell lymphoma</td>
<td>Usually negative</td>
<td>Usually positive: CD19, CD20, CD79a&lt;br&gt;Occasionally positive: sIg</td>
<td>TdT: Negative&lt;br&gt;CD30: Occasionally positive</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma</td>
<td>Occasionally positive: CD4, CD8, CD3 (surface)</td>
<td>Usually negative</td>
<td>CD30: Usually positive&lt;br&gt;Alk: Usually positive</td>
</tr>
<tr>
<td>Peripheral T cell lymphoma</td>
<td>Usually positive: CD4, CD8, CD5, CD7, CD3 (surface)&lt;br&gt;Usually negative: CD1a</td>
<td>Usually negative</td>
<td>CD30: Occasionally positive&lt;br&gt;Alk: negative</td>
</tr>
</tbody>
</table>
Prognostic Factors

In NHL, staging systems have been used to identify groups of patients with diverse prognoses. The most commonly used, a system introduced by St. Jude Children’s Research Hospital, applies to all subtypes of NHL (Table 1).16

Table 1: The St. Jude Staging System for NHL in Children

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A single tumor (extranodal) or single anatomic area (nodal), excluding mediastinum or abdomen</td>
</tr>
</tbody>
</table>
| II    | □ A single tumor (extranodal) with regional node involvement,  
       | □ On same side of the diaphragm:  
       | (a) Two or more nodal areas  
       | (b) Two single extranodal tumors, with or without regional node involvement  
       | □ A primary gastrointestinal tract tumor (usually ileocecal) with or without associated mesenteric node involvement, grossly completely resected |
| III   | □ On both sides of the diaphragm:  
       | (a) Two or more nodal areas  
       | (b) Two single extranodal tumors  
       | All primary intrathoracic tumors (mediastinal, pleural thymic)  
       | □ All extensive primary intra-abdominal disease; unresectable  
       | □ All primary paraspinal or epidural tumors, regardless of other sites |
| IV    | Any of the above with initial CNS or bone marrow involvement (< 25%) |

Its main value is in separating patients with localized disease from those with advanced disease. More recently, information on immunophenotype and molecular findings has been incorporated into classification schemes. This approach has established a foundation on which investigators can develop treatment regimens specific to immunophenotype and disease stage.

Recently many groups of investigators have used LDH level as a surrogate value for tumor burden in making treatment decisions regarding B-cell NHL.
Response to therapy has been used similarly. In patients with B-cell lymphoma, French investigators have proposed the use of imaging studies to estimate the reduction in tumor mass after one week of cyclophosphamide, vincristine, and prednisone treatment. Patients whose primary tumor was reduced by less than 20% received more intensive treatment. Recently gene chip arrays have been developed to identify molecular features associated with NHL. Whether this method will add meaningful prognostic information remains to be determined.

The most important prognostic factor in pediatric NHL is an accurate diagnosis and evaluation of the extent of disease, so every effort should be made to correctly characterize disease biology before treatment.

**Treatment**

Progress in the treatment of children and adolescents with NHL parallels that of childhood acute lymphoblastic leukemia. Investigators of most contemporary clinical trials report survival estimates approaching 90%. Moreover, the relevance of clinical and biologic prognostic factors has been practically eliminated by the use of risk-adapted strategies specific to disease stage and immunophenotype in conjunction with a wide range of effective agents, which are largely responsible for the improved survival estimates.

Treatment has emerged as the single most important determinant of successful outcome of NHL. Clinical and biologic features that guide the therapeutic strategy include the extent of the disease at the time of diagnosis, sites of involvement, immunophenotype, morphology and immunohistochemistry of tumor cells, and early response to therapy. Treatment for pediatric lymphomas is usually based on the biology and disease extension.

Even though many studies performed in the eighties showed that patients with localized (stages I and II) lymphoma have an excellent outcome regardless the histopathology when treated with moderately intensive chemotherapy, most
current studies treat differently patients with localized B cell lymphoma, lymphoblastic lymphoma and anaplastic large cell lymphoma. Patients with low-risk NHL (approximately 20% to 30% of pediatric cases), have an excellent prognosis, with a probability of survival of more than 90%, after treatment with two or three courses of chemotherapy. The Pediatric Oncology Group, which conducted several studies of stage I or II NHL, came to the following conclusions: (1) local radiotherapy can be safely omitted; (2) chemotherapy cycles of moderate intensity (four agents) are sufficient to eradicate NHL; (3) chemotherapy should last no longer than 6 months; (4) CNS-directed therapy is indicated only for patients with primary tumors in the head and neck region; and (5) lymphoblastic lymphoma, which accounts for only 10% to 15% of the cases of limited-extent disease, requires maintenance chemotherapy (daily doses of 6-mercaptopurine and weekly doses of methotrexate). Similar results have been achieved by other pediatric cooperative groups using modified versions of the St. Jude staging system.

We therefore describe the guidelines for treatment for the three major subtypes of pediatric lymphoma.

**Lymphoblastic lymphoma**

Investigators developing treatment for lymphoblastic NHL have assumed that this form of the disease behaves the same as does T-cell ALL. Their assumption is based on results of the seminal Children’s Cancer Group study, reported more than 20 years ago, showing that the LSA2L2 regimen, an ALL-type therapy, was significantly more effective than pulse chemotherapy (COMP) in the treatment of lymphoblastic NHL. However, because most lymphoblastic NHL is of T-cell immunophenotype, ALL regimens that have not been particularly successful in the treatment of T-cell ALL are expected to yield poor results in the treatment of lymphoblastic NHL. The BFM-90 protocol for NHL incorporates treatment components found to be effective in T-cell ALL.
This treatment was associated with a 5-year event-free survival (EFS) estimate of 92% in more than 100 patients with lymphoblastic lymphoma—a truly remarkable achievement. Even though no single component of treatment can be considered essential for the treatment of lymphoblastic lymphoma, most protocols include an induction phase, including steroids, vincrsitine, anthracyclines and L-asparaginase followed by a consolidation phase with cyclophosphamide, cytarabine, and 6 mercaptopurin and then an extracompartiment phase, usually including high dose methotrexate and finally a re-induction phase followed by maintenance with 6 mercaptopurin and oral methotrexate to complete 18 to 24 months of treatment. Patients without overt CNS disease may not require cranial irradiation provided that a regimen including adequate intrathecal therapy and high dose methotrexate was given. A recent BFM trial (NHL-BFM 95) showed that patients who did not receive cranial radiotherapy had no inferior outcome than their irradiated historical cohort from their previous study.57 Patients with overt CNS involvement should be given 18 to 24 Gy of cranial radiotherapy. Patients with localized lymphoblastic lymphoma are very uncommon, but there is enough evidence to support the withdrawal of the reinduction treatment in this subgroup. Nevertheless, maintenance therapy and CNS prophylaxis is needed.

Besides from stage, it was difficult to find any prognostic factor in lymphoblastic lymphoma. In recent years, BFM investigators found that female patients older than 10 years had a poorer outcome and those with chromosome 6q deletions also had a higher probability of relapse.58,59
B-cell malignancies

In this subgroup, children with Burkitt lymphoma, B large cell lymphoma and those with mediastinal (thymic) large B cell lymphoma with sclerosis are treated with the same strategy regardless their biological differences. Treatment intensity is tailored according to disease extension. So, patients who are not classified as having limited or low-risk disease are collectively grouped as high-risk patients. Naturally, patients placed in this category have a wide range of tumor burdens and are likely to have diverse prognoses. Due to this diversity, treatments vary greatly on the basis of the staging system used. For example, a patient with Burkitt lymphoma without CNS involvement and < 25% blast cells in the bone marrow is considered to have stage IV disease according to the St. Jude system; but the patient is placed in group B in the French Society of Pediatric Oncology (SFOP) staging system, which stipulates 70% or more of bone marrow involvement for group C. Treatment of group C disease is much more intensive than that of group B.\textsuperscript{23}

In general, patients with advanced B-cell malignancies are treated with high dose, fractionated and relatively short-duration chemotherapy regimens. Since these tumors are exquisitely sensitive to chemotherapy, acute tumor lysis may occur after the initial treatment so, a cytoreductive pre-phase is usually needed to allow for a gradual reduction of the tumor burden. The current regimens used for the treatment of B-cell malignancies were designed by two cooperative groups: the French Society of Pediatric Oncology (SFOP) and the german, Austrian, Swiss BFM studies. In recent years, an international group for the treatment of B cell lymphoma was created with the participation of French, North American, British and other European countries (FAB group). Large randomized studies were done by this group and some controversial issues could be ascertained. A recent report from this group showed that the survival rate for patients with localized disease was 99% with only two cycles of chemotherapy.\textsuperscript{60} One of the most important findings was that therapy could be
safely reduced in group B patients (which comprised about 70% of the cases). In their study, patients with group B, defined with one modification: bone marrow involvement should be less than 25%, instead of 70% as stated above, that had a good initial response to initial therapy were randomized in a sequential fashion to receive a less intense therapy half the dose of cyclophosphamide and the omission of the maintenance course. No difference was seen compared with the standard group and the probability of event-free survival was over 90% in all arms.

Other investigators define risk categories associated with advanced-stage disease on the basis of serum LDH concentrations. Berlin-Frankfurt-Munster (BFM) protocols also stratify patient groups according to their LDH values. In the most recent protocol from this group, a critical role of methotrexate for the treatment efficacy in B-cell malignancies was detected. In patients with localized disease, 1 gram/m2 of methotrexate infused over 4 hours proved to be less toxic and no less effective than their standard dose of 5 grams/m2 infused over 24 hours. However, when patients with advanced disease were considered, patients who received the standard 5 grams/m2 dose had a significantly better outcome than those children with shorter duration infusions. However, those receiving the shorter duration infusions had significantly less treatment-related toxicity. This finding could be important for developing countries where treatment toxicity causes significant mortality. In BFM studies, those patients whose LDH values exceed 1,000 U/L were at highest risk and received a more intensive therapy. However, because what is considered a normal range of LDH values may vary by institution, relative, rather than absolute values of LDH should be considered as a basis for making treatment decisions. Therefore, other investigators in cooperative groups used an elevation of LDH greater than 2 times the institutional normal values as a basis for stratification of patient groups.
The highly successful protocol (LMB89)\textsuperscript{18} developed by French investigators to treat B-cell NHL (Burkitt, Burkitt-like, and large B-cell lymphomas) has become the benchmark for other protocols. For such subtypes, intensive, high-dose treatment of short total duration (5 to 8 months) and a reduced interval between treatment cycles are the hallmark of all effective types of combination therapy. CNS-directed therapy is mandatory, and patients with evidence of CNS involvement or those in the high-risk category should receive intensive therapy. However, cranial radiotherapy is not needed for CNS prophylaxis or treatment in patients with B-cell malignancies. Patients with Burkitt lymphoma and CNS invasion have a poorer prognosis. However, recent studies from the BFM and FAB groups reported an improved outcome with the use of intensive systemic chemotherapy and intraventricular (via an Omaya reservoir) from the BFM or intensified intrathecal therapy for the FAB studies.\textsuperscript{64,65} Treatment of patients with B large cell lymphoma should follow similar guidelines as for patients with Burkitt’s lymphoma. Despite most adult studies include CHOP and rituximab as the standard for treatment of large cell lymphoma, this combination has not sufficiently tested in children.\textsuperscript{66} Patients with large B cell lymphoma in children usually present with localized nodal disease and the results in terms of survival and morbidity with the use of the same regimens as for Burkitt lymphoma are excellent. Patients with mediastinal (thymic) B cell lymphoma with sclerosis have a poorer prognosis and are discussed below in a separate section.

**Anaplastic large cell lymphoma**

The third largest group of childhood NHL (ALCL) comprises approximately 15\% of all cases of pediatric NHL, and it includes tumors with T-cell markers or a null-cell immunophenotype.\textsuperscript{26} Because the clinical and biologic characterization of this NHL subtype is still evolving, treatment programs for this disease have differed vastly.
Only a few pediatric cooperative treatment groups have reported results of studies in which patients were selected by using the contemporary definition of ALCL: co-expression of CD30 and the epithelial membrane antigen in cells with T-cell or null immunophenotype. Remarkably, the results, albeit inferior to those noted in pediatric B-cell or lymphoblastic NHL, have shown that approximately 60% to 80% survival rates can be achieved with either treatment strategy.

The French Society of Pediatric Oncology used a protocol based on the treatment of B-cell NHL that prescribes 2 cycles of COPDAM (methotrexate, cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by 5 to 7 months of maintenance chemotherapy. Complete responses were achieved in 95% of the patients; 21/82 patients experienced an adverse event. By using a strategy developed for B-cell NHL, BFM investigators reported improved results. The 5-year EFS estimate for 55 patients with stage III disease was 76%; for 6 patients with stage IV NHL, 50%. In the BFM study, treatment lasted only 5 months; in the others, 10 to 24 months.

However, other groups used other treatments with comparable results. Using a strategy based upon the LSA2L2 regimen, the Italian Cooperative Group AEIOP reported 65% event-free survival figures. A comparable survival outcome was found by the POG by using the APO regimen, which is based mostly upon doxorubicin. A recent international study was carried out using the BFM backbone and randomizing two different doses and schedules of methotrexate as well as the value of maintenance with vinblastin but the results are not available yet. It has been difficult to find prognostic factors for pediatric ALCL, probably because the different treatment schemas that were used. A recent analysis of a large European intergroup including 225 patients treated under comparable treatment strategies revealed that mediastinal, skin and visceral involvement were the most important prognostic factors.
The relative value of stage (St Jude or Ann Arbor) in this variety of pediatric lymphoma is uncertain, mostly because the difficulty of assigning a proper stage to the common extranodal locations in this malignancy.

Salvage Therapy (Partial Responses or Relapse)

Persistent or relapsed NHL presents serious management problems. Because contemporary, risk-directed therapies are usually very intensive, the overall prognosis for such cases is dismal.

In patients with a residual mass after induction and consolidation therapy, persistent disease should be confirmed by biopsy, as imaging studies commonly detect nonviable tumor. The diagnosis of persistent active disease in patients with residual masses can be challenging, since it can be difficult to differentiate viable residual cells from necrotic or apoptotic cells in resected residual masses.

When persistent disease during therapy or relapse is documented, the options for salvage therapy depend on the intensity and types of agents used in the primary therapy, histologic disease type, and timing of the relapse. Because primary therapy for Burkitt lymphoma or large B-cell lymphoma includes most of the known effective agents, salvage therapy is usually based on regimens containing cisplatin or carboplatin, such as the widely used combination of ifosfamide, carboplatin, and etoposide. Monoclonal antibodies to B-cell antigens, successfully used to treat B-cell lymphomas,²⁸ have been combined with conventional chemotherapy or conjugated to radioisotopes. The monoclonal anti-CD20 (rituximab), for example, has been widely used in combination with standard chemotherapy.

Because a second complete response to non-cross-resistant chemotherapy regimens, if achieved, is usually short, HSCT is recommended.
The principles of management of relapsed lymphoblastic NHL are similar to those of relapsed ALL. When a second remission is achieved, HSCT is also indicated. The outcome of residual disease after salvage therapy is very poor.

Contrary to what is observed in Burkitt and lymphoblastic NHL, in ALCL, second remission is usually possible. Salvage treatment has included intensive chemotherapy with or without HSCT. In a recent SFOP study, a second remission was achieved in 36 of 41 cases of relapsed ALCL.29 Eight of 13 patients receiving a single agent, (vinblastine administered weekly) experienced prolonged remission, which suggests that several relapses of ALCL do not preclude a long period of disease-free survival. BFM investigators have reported the use of allogeneic BMT for 20 patients with relapsed/resistant ALCL.30 Event-free survival 3 years after BMT was 75%; and outcome was not influenced by donor type or conditioning regimens.

**Supportive Care**

Patients with lymphoid malignancies often present with respiratory, cardiovascular, neurologic, renal, hemorrhagic, infectious, and metabolic complications. Intense tissue remodeling—cell proliferation and cell death—results in a large tumor burden and rapid turnover of nucleoproteins, both of which are responsible for the dysfunction of these organ systems. The rate of mortality due to these complications has been reduced to less than 1% by prompt recognition of signs and symptoms, careful clinical and laboratory evaluation to determine the presence of these complications, and early intervention. Mortality resulting from these complications is defined as death not due directly to the leukemia or lymphoma.
Respiratory distress from compression of mediastinal structures is common in lymphoblastic NHL. Compression of the vessels of the mediastinum can lead to intraluminal thrombosis and sudden death. In cases of severe compression, general anesthesia is not recommended because of an increased risk of complete, irreversible airway block. In an emergency it is sometimes necessary, before diagnosis is made, to reduce the risk of airway compression by administration of corticosteroids or local radiotherapy (or both).

**Figure 1:** Massive airway compression caused by mediastinal lymphoblastic lymphoma.⁷⁵
Massive ascites and intra-abdominal involvement in Burkitt lymphoma can cause compression of the bowel and ureter\textsuperscript{31}. In addition, abdominal blood and lymphatic vessels can become compressed, which results in reduced blood flow and lymphatic return and in edema of the lower extremities. Small bowel perforation may occur during induction of patients with abdominal Burkitt lymphoma.\textsuperscript{70}

Patients with NHL are at particularly high risk of biochemical complications because of the high rate of cell turnover and the high sensitivity of the malignant cells to chemotherapy. Biochemical abnormalities, often present before chemotherapy begins, are induced by fever, processes associated with infection, dehydration, and even spontaneous cell lysis. These metabolic abnormalities, which include hyperuricemia, hyperphosphatemia, hypocalcemia, hyperkalemia, and azotemia, characterize tumor lysis syndrome (TLS). The pathogenetic consequences of this syndrome result from the release of cellular breakdown products that exceed the hepatic and renal anabolic and catabolic capacities. The deposition of phosphorus, uric acid, and its precursors (hypoxanthine and especially xanthine or both) in the lumina of the renal tubules is believed to be central to the development of renal insufficiency. If these metabolic abnormalities become severe, renal failure, cardiac arrhythmia, respiratory distress, and death can follow.

Features associated with increased risk of TLS include hyperleukocytosis, massive organomegaly, renal enlargement, extrinsic compression of the genitourinary tract, and elevated serum LDH activity. Patients with established TLS or those at high risk for TLS should be monitored carefully. Preferably, they should be admitted to an intensive care unit and cared for by a multidisciplinary team. The team must ensure adequate urinary flow before chemotherapy is started. To determine the adequacy of renal function, a slightly hypotonic solution without potassium should be administered intravenously at a rate of 2 to 5 L/m\textsuperscript{2} per day.
Administration of fluids dilutes intravascular solutes such as urates and phosphates, increases renal blood flow and glomerular filtration, and flushes precipitated solutes from the renal tubules. The availability of recombinant urate oxidase (rasburicase) has greatly facilitated the prevention and management of hyperuricemia.³²

**Uncommon Forms of Pediatric non-Hodgkin Lymphoma**

Although the overwhelming majority of patients with pediatric lymphoma fall into the three categories, (Burkitt, lymphoblastic and large cell), some patients occasionally present with less common disease subtypes that pose diagnostic and treatment challenges. Many times, pathologists in children’s hospitals do not have the experience or reagents needed to precisely characterize these uncommon forms of lymphomas. It is crucial for pediatric oncologists to have a high index of suspicion for these rare lymphomas, and collaboration among pediatric and adult pathologists is often necessary to reach the correct diagnosis.

*Follicular NHL*

Follicular pediatric NHL, which occurs in about 3% of all pediatric cases, differs substantially from its adult counterpart.¹⁰,³³,³⁴ In adults, follicular NHL is disseminated, has a low histologic grade, and is incurable with current therapies. Conversely, pediatric NHL is typically localized with intermediate or high histologic grade (grade 2 or 3), and highly curable. Pediatric cases are more common in males. Head and neck lymph nodes or tonsils are the most common primary sites. Extranodal sites include the gastrointestinal tract, parotid, kidney, epididymis, and testes. Approximately 70% of the pediatric cases have localized (Stage I or II) disease. CD10 is expressed in most tumor cells; in a minority, CD34 is expressed.
The Bcl-6 protein is frequently present, although the Bcl-2 protein is not. Furthermore, in contrast to the adult counterpart, in the most cases of pediatric follicular NHL, the t(14;18) rearrangement is not present.

NHL involvement of the testes is rare; most involvement is present at diagnosis in patients with disseminated lymphoblastic or Burkitt NHL. Primary testicular lymphoma is usually of follicular histiotype. Of the approximately 12 cases reported the median age at diagnosis was 5 years; tumors were small (2-4 cm), and the histologic grade was III. CD10 was expressed in 6 of 9 cases tested, and the Bcl-6 protein was expressed in 10 of 11 cases tested. The Bcl-2 protein was not expressed in any of the cases tested, and the t(14;18) rearrangement was not evident in 8 cases tested.

The treatment of pediatric follicular NHL is controversial. Investigators from the United Kingdom Children Cancer Study Group (UKCCSG) have even suggested that children with localized and completely resected tumors do not need further therapy. Their recommendation is based on a very small number of patients. Patients with more advanced disease or those who had incomplete resections received a short course of chemotherapy in accordance with the UKCCSG protocol 10. At St. Jude, patients with follicular NHL are treated according to disease stage. Patients with Murphy disease stage I or II receive chemotherapy as prescribed by the Pediatric Oncology Group. Those children with the rare diagnosis of advanced-stage follicular NHL usually receive more intensive treatment.

**Marginal Zone B-cell Lymphomas**

Marginal zone lymphomas are relatively rare forms of B-cell malignancies derived from post-germinal B-cells. They are much more common in older patients (median age, 60 years) than in children or in young adults. Pediatric cases are very rare and have been associated with autoimmune disorders such as Sjögren syndrome, Hashimoto thyroiditis, and systemic lupus erythematosus.
The primary site varies considerably and includes nodal and extranodal regions. Approximately 8% to 10% of adult cases of NHL are classified as extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type (MALT). The stomach is the most commonly affected among the extranodal sites. Other extranodal sites include the salivary glands, orbit, and lungs. In the etiology of MALT-associated gastric lymphoma, infection with the bacterium *Helicobacter pylori* has been implicated. Isolated cases of MALT lymphoma have been reported in pediatric patients who are HIV-infected. Only four patients (<0.1%) of the 2,703 admitted on NHL BFM studies between 1986 and 2004 received a diagnoses of MALT lymphoma. All four cases had extranodal sites: lower lid, breast, conjunctiva, and stomach. In another, 32 of 48 children and young adults with marginal zone B-cell lymphoma (67%) had nodal presentation. They ranged in age from 2 to 27 years (median, 16 years); 21 patients (66%) were 18 years of age or younger and the disease predominated in males.

Most patients (88%) presented with isolated, painless, peripheral adenopathy in the head and neck region that lasted from a few weeks to 2 years. None of these patients were HIV positive or showed signs of autoimmune disorder. In 19 of these patients, examination of bone marrow did not indicate the presence of tumor. Only one patient had stage III disease, with cervical, supraclavicular, and mesenteric nodes involvement. Treatment approaches varied among 28 patients. Surgery only, with completely excised tumors, was reported in 19 patients; 5 received local radiotherapy; 3 received systemic chemotherapy; and 1 patient received a combination of radiotherapy and chemotherapy.

Only one disease recurrence was reported, and that was in a patient who underwent surgery and received no other treatment. At the time of the report (four years of follow-up), the patient was free of disease. Sixteen of the 48 patients (33%) had extranodal marginal zone lymphoma.
The median age was 24.5 years, 4 of 16 cases were pediatric, and there was no gender preponderance. The most common disease sites at presentation were the ocular adnexa (5 of 16, 31%), the salivary glands (4 of 16, 25%), and skin (3 of 16, 19%). Only one patient had gastric involvement. Three patients with salivary gland involvement (two females) had a history of autoimmune disease. Two had Sjögren syndrome, and one had systemic lupus erythematosus. In addition, the single patient with gastric involvement had a history of *Helicobacter pylori* gastritis and gastric ulcers.

More than 70% of evaluable patients had stage I disease. Concomitant regional lymph node involvement was evident in two cases, but dissemination to other nodal or extranodal sites was not observed. In all five cases in which bone marrow was examined, involvement was not present.

Information on treatment and outcome was available for nine patients. Five were treated with local radiotherapy, two with excision alone, and two with chemotherapy. Follow-up ranged from 1 to 24 months. Only one patient experienced a local relapse of disease. He had a large conjunctival mass at presentation, and had been treated with excision only. The accurate diagnosis of these conditions requires experienced pathologists and sophisticated immunologic and molecular diagnostic tools often not available in developing countries. In this setting, the treating physician should also consider that other more common types of lymphoma may extend to the stomach, orbit, and tonsils. Therefore, every effort should be made to biologically characterize these lymphomas to ensure adequate treatment.
Mature T- and Natural Killer-cell non-Hodgkin Lymphomas

The clinical features and outcome of children with mature T cell malignancies in children is less known than their precursor cell counterpart. Despite many randomized studies including large cohorts of children with Burkitt, lymphoblastic and ALCL have been reported, little is known about the mature or also known as peripheral T cell lymphomas. Several subtypes described below comprise this subgroup but it is not unusual to see some cases where it is impossible to assign a specific subtype and the child is categorized as peripheral T cell lymphoma non further specified. The prognosis of this child is usually dismal, but current survival features show better results.71 There is no consensus about the best treatment strategy for these malignancies but a similar strategy to the one used for precursor T cell lymphomas is generally used.

Primary Cutaneous CD30+ T-cell Lymphoma

Primary cutaneous CD30+ anaplastic large T-cell (ALTC) lymphoma is rarely seen in children. It is part of a spectrum of closely related lymphoproliferative disorders such as lymphomatoid papulosis, mycosis fungoides (Figure 1), and subcutaneous panniculitis-like T-cell lymphoma (Figure 2)(Table 3)39–41. Most patients with CD30+ALCT present with isolated or multifocal nodules, papules, or tumors that are frequently ulcerated. Multifocal lesions are seen in approximately 20% of the patients. The skin lesions may regress spontaneously, but they do not wax and wane as do those in lymphomatoid papulosis. Disease extension to other organs is rare (10%) and typically involves the lymph nodes.

The prognosis of CD30+ ALTC is favorable (Figure 3). Conversely, children with systemic CD30+ large cell lymphoma with secondary skin involvement have much worse prognosis and require intensive systemic chemotherapy.
<table>
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<td><strong>Primary Cutaneous</strong></td>
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<td>Anaplastic large cell lymphoma</td>
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<td>Lymphomatoid papulosis</td>
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<td>Epidermotropic CD8 + T-cell lymphoma</td>
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<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
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Figure 1
Figure 2: Subcutaneous nodules of panniculitis like T-cell lymphoma. These nodules underwent a wax and wane presentation.
Lymphomatoid papulosis is a chronic condition characterized by recurrent papulonecrotic skin lesions that wax and wane. Its malignant nature has not been definitively proved. However, progression to cutaneous ALTC has been documented. Lymphomatoid papulosis has also been associated with other types of malignancy, including Hodgkin disease. The typical lesions, which can be localized or generalized, are red-brown papules and nodules in different stages of evolution. The lesions evolve with central hemorrhage, necrosis, and crusting, and wax and wane (the hallmark of this condition).
The pathologic distinction between lymphoid papulosis and cutaneous CD30+ ALTC is often difficult to see; therefore, the dermatologic features and natural history have usually been used to make that distinction.

No uniform guidelines have been developed for the management of these interrelated disorders. The correct diagnosis and classification are crucial to treatment planning. Being able to distinguish between primary cutaneous CD30+ ALTC and systemic large cell lymphoma with secondary cutaneous involvement requires careful disease staging. For primary cutaneous ALTC, the type of treatment depends on the extent of the disease. A solitary or a few regional lesions can be treated with local radiotherapy. If a solitary lesion has been completely excised, no further treatment is recommended, unless it recurs. Some of these cases of primary cutaneous ALTC and those involving residual disease can be treated with a short course of chemotherapy such as that used for low-stage NHL.22

Management of multifocal primary cutaneous ALTC is controversial. Intensive chemotherapy has been used, but it appears to be ineffective. In some cases, low-dose methotrexate has been successfully used. A treatment regimen for lymphomatoid papulosis has not been defined. Intensive chemotherapy or radiotherapy is not indicated because the lesions will reappear after a period of “remission.” When the lesions regress without scarring, specific treatment is not necessary. When scarring occurs, low-dose methotrexate can be administered orally.

Extranodal NK/T-cell Lymphoma, Nasal Type

Nasal extranodal NK/T-cell lymphoma, a distinct clinicopathologic entity, is characterized by chronic midfacial processes42-43. It most commonly presents clinically as a destructive nasal or midline facial tumor within one year of evolution.
The lesion usually develops in the nasal cavity, causing nasal obstruction, rhinorrhea, epistaxis, and facial edema. Palatal destruction and orbital swelling may also occur. Less commonly, extranodal NK/T-cell lymphomas involve cervical nodes, skin, soft tissues, testicles, and the gastrointestinal and respiratory tracts. Other names by which this entity is known include Stewart granuloma, lethal midline granuloma, angiocentric lymphoma, idiopathic midline destructive disease, pseudolymphoma, malignant midline granuloma, non-healing midline granuloma, polymorphic reticulosis, and lymphomatoid granulomatoses. It occurs more often in male patients in Asian and Central American countries and Native Americans. This disease is highly associated with EBV. In the early stages, extranodal NK/T-cell lymphoma is difficult to characterize histologically. The lesion is composed of an atypical polymorphic infiltrate with a broad spectrum ranging from small cells to large transformed cells with a propensity to invade and destroy blood vessels. In situ hybridization studies with probes to EBV-encoded small nuclear RNA can detect even small numbers of neoplastic cells; such studies are invaluable in diagnosis. Analysis of immunohistochemistry usually reveals T cell-associated antigens, including CD2, the intracytoplasmic CD3-ε chain, and the NK-associated antigen CD56. Results of molecular studies do not indicate the presence of the T-cell gene rearrangement in malignant cells.

Treatment of extranodal NK/T-cell lymphoma is still evolving. Anthracycline-based therapy plus local radiotherapy is typically used. Because the disease is rare in children and adolescents, prognostic factors have not been established in this age group. In adults treated with chemotherapy and radiotherapy, predictors of poor outcome include constitutional “B” symptoms, high lactated dehydrogenase levels, and regional nodal involvement. Patients without any of the risk factors (localized disease) had an approximately 50% probability of survival, whereas patients with disseminated disease had a dismal outcome.41
Figure 4: Clinical appearance of a patient with extranodal NK/T-cell lymphoma (nasal type).

Aggressive NK-Cell Leukemia

Aggressive NK-cell leukemia is characterized by a fulminant clinical course. Immunophenotype and molecular genetic findings are similar to those of nasal-type NK/T-cell lymphoma. Patients are typically from Asian countries who present with fever, hepatosplenomegaly, leukopenia, and coagulopathy. This may lead to multiple organ failure followed by death within weeks of the initial signs and symptoms. As was the case with extranodal NK/T-cell lymphoma, aggressive NK-cell leukemia is highly associated with EBV.
A closely related condition also seen in children and adolescents has been designated EBV+ fulminant T-cell lymphoproliferative disorder (fatal mononucleosis). It can occur after acute EBV infection, or more commonly after chronic EBV infection. However in this case, the malignant cells express true T-cell immunophenotype, including expression of clonality by rearranged T-cell receptor studies. In a manner similar to that of aggressive NK-cell leukemia, fatal mononucleosis is also characterized by severe hemophagocytic syndrome, from which the patient usually dies.

**Hepatosplenic T-cell Lymphoma**

Hepatosplenic T-cell lymphoma is a rare, extranodal, and usually fatal, disorder resulting from the malignant transformation of cytotoxic T-cells, usually of $\gamma\delta$ T-cell receptor type. It occurs very rarely in children and most often affects young adults. Typically, patients with hepatosplenic T-cell lymphoma present with marked hepatosplenomegaly and various degrees of cytopenia. Adenopathy and circulating blasts are usually absent. Bone marrow involvement is frequent. The neoplastic cells, typically $\gamma\delta$ T-cells, are present in the sinusoids of the bone marrow. In most cases, CD4 and CD8 are not expressed in neoplastic cells, while CD56 is. Also, TIA-1, a cytotoxic T-cell marker, is usually expressed. T-cell variants with an $\alpha\beta$ phenotype have been described as well. Isochromosome 7q and trisomy 8 are consistent cytogenetic abnormalities.

Although a few cases have been successfully treated with chemotherapy alone, the overall prognosis of this disease is dismal. Hematopoietic stem cell transplantation (HSCT) has been effective in a small number of patients.
Primary Mediastinal Large B-cell Lymphoma with Sclerosis

Primary mediastinal large B-cell lymphoma with sclerosis (PMLBCL) has been recently recognized as a distinct clinicopathologic entity with a molecular gene-expression signature reminiscent of nodular sclerosis subtype of classical Hodgkin disease. Although it develops more commonly in adults, it can develop in children, predominantly adolescent girls.

Tumor cells arise from the medullary thymic B cells and often express CD79a, CD19, CD20, and CD22, but not surface immunoglobulin or BCL 6. Patients often present with a rapidly growing mediastinal (thymic) mass, usually without involvement of other areas; the kidney may also be involved.

Limited information is available on this disorder in children. In adults, regimens with polychemotherapy combined with local radiotherapy were used. Other adult studies suggest a benefit from therapy intensification and autologous stem cell rescue. The BFM group reported its experience in successive trials (30 patients) in which results were relatively poorer than those of studies of other types of B-cell malignancy. The group reported a probability of event-free survival of 0.7 for the whole group, and elevated LDH values were correlated with prognosis. Therefore, the most effective treatment of this condition in children it is not currently known, and the utility of radiotherapy is debatable.

Treatment of Non-Hodgkin Lymphoma in Developing Countries

Pediatric NHL in developing countries is associated with some peculiarities. In an INCTR study, Naresh et al. evaluated the distribution of lymphomas in several developing countries and found regional variation of subtypes. The archetypical example is Burkitt lymphoma, which is endemic to Equatorial Africa, and which typically involves the jaw or the orbit in younger children (Figures 1 and 2).
In Africa, Burkitt lymphoma accounts for 45% of all cases of childhood malignancy. In Africa and other developing areas of the world treatment is still inadequate. For example, in Malawi, only approximately 50% of children with localized Burkitt lymphoma survive disease free, in sharp contrast with the greater than 90% survival estimates of comparable groups of patients in the developed countries.

**Figure 1**
To improve the outcome in Malawi, the International Society of Pediatric Oncology (SIOP) launched a series of studies in which attempts to use a modification of the high-dose regimens proposed by the SFOP caused unacceptable number of deaths due to toxicity and had to be discontinued. A low-intensity regimen is prescribed in this setting because of poor patient tolerance caused by malnutrition, malaria, parasitosis, and lack of compliance for longer therapies.
Although many African children with NHL have no access to chemotherapy, encouraging results have been reported in South Africa. A recent report from a cooperative group sponsored by French investigators showed improved results with more than 60% survival from 6 African countries. In other emerging nations, non-Hodgkin lymphoma also represents a challenge. In some Latin American countries, such as Brazil and Argentina, encouraging results have been reported by those using adapted BFM therapies. Current survival figures for B-cell malignancies are in the range of 80-85% in reference centers. In Turkey and Venezuela, SFOP protocols have been used with similar results. However, death due to toxicity is higher than that reported in developed nations. Physicians working in developing countries should also consider that B-cell lymphoma might behave differently in their areas and that treatment tailored to these differences should be developed. The information about other lymphoma subtypes is more limited.

In developing countries, only tertiary-care centers can provide the quality of care needed for patients with B-cell lymphoma when they receive high intensity therapy. In the developed nations, uncommon subtypes might be more prevalent than in developing countries. In some Latin American countries, hydroa vacciniforme such as skin lymphoma has long been recognized and has recently been included in the WHO-EORTC classification for skin lymphomas. In Asia, NK-cell malignancies are more frequent.
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