Non-Hodgkin’s Lymphomas

MICHAEL GRAHAM, MD

The non-Hodgkin’s lymphomas of childhood and adolescence are a heterogeneous group of diseases that constitute 7% to 10% of pediatric malignancies. These tumors rank third in frequency behind leukemias and CNS tumors. The lymphomas are mostly seen in children over 5 years of age, with a male to female distribution of 3:1.

Major differences between the types of lymphomas seen in children and adults allow for a simplified classification of childhood lymphomas. The commonly used classification systems for adult lymphomas each list at least 15 entities. However, over 90% of pediatric lymphomas have been conveniently categorized by Murphy into lymphoblastic, undifferentiated Burkitt’s, undifferentiated non-Burkitt’s, and large cell (histiocytic) types. Lymphomas in children tend to exhibit aggressive behavior with a propensity for widespread dissemination. These tumors are quite responsive to treatment, however, resulting in high cure rates for certain types.

ETIOLOGY

The etiology of non-Hodgkin’s lymphomas is the subject of intense research. As is the case for most childhood neoplasms, the causes of individual cases of non-Hodgkin’s lymphomas can seldom be determined. Several factors, including viral infections and immunodeficiency, may play a role.

The Epstein-Barr (EB) virus has been linked to the development of Burkitt’s lymphoma in children in Africa, where this type of cancer is endemic. Tumor cells from these patients often have viral DNA and nuclear antigens, and patients have high antibody titers against the EB virus. The form of Burkitt’s lymphoma commonly seen in non-African children, however, only occasionally shows an association with the EB virus.

Many patients with human immunodeficiency virus (HIV) infection also have non-Hodgkin’s lymphomas. Likewise, some adults (no children to date) with T cell lymphoma and leukemia have been shown to have disease caused by the human T cell lymphotropic virus (HTLV-1).

The exact mechanisms by which viral infections are linked to the development of lymphomas remains to be determined. Some exciting work has shed light on the molecular changes accompanying lymphomatous transformation. Most cases of Burkitt’s lymphoma show a translocation of a segment of the long arm of chromosome 8 to chromosome 14 (Figure 1); other cases have translocations from chromosome 8 to either chromosome 2 or 22. The translocated portion of chromosome 8 contains the c-MYC gene. When translocated, the c-MYC gene does not respond to usual cellular controls. In this way it may contribute in

Dr. Graham is Assistant Professor of Pediatrics, School of Medicine, Johns Hopkins University, Oncology Center, Johns Hopkins Hospital, Baltimore, Maryland.
Address reprint requests to Dr. Michael Graham, Oncology Center, Room 3121, Johns Hopkins Hospital, 600 N. Wolfe Street, Baltimore, MD 21205.
producing the neoplastic changes. 

Children with immunodeficiency disorders who sometimes develop non-Hodgkin's lymphomas include those with Wiskott-Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency, and Bloom's syndrome. In addition, patients undergoing immunosuppression following renal transplantation have a high risk of developing lymphomas. The connection between immunodeficiency and lymphomas remains unclear. However, some experimental and epidemiologic studies suggest that chronic immunostimulation by an infectious agent may cause uncontrolled proliferation of lymphoid cells, which may eventually lead to lymphomatous transformation. 

HISTOLOGIC AND IMMUNOLOGIC CLASSIFICATION

The division of non-Hodgkin's lymphomas into subtypes has been greatly simplified. More than 90% of children with these tumors can now be classified as either large cell, lymphoblastic, undifferentiated-Burkitt's, or undifferentiated non-Burkitt's types (Table 1). Furthermore, some have questioned the need for distinction between the Burkitt's undifferentiated and non-Burkitt's undifferentiated types.

Malignant lymphoma cells often retain certain surface and functional features similar to those of non-malignant lymphoma cells. Thus, lymphoma cells and leukemia cells are often categorized using laboratory techniques that distinguish among B cells, T cells, and non-B, non-T or null cells. In general, B cells are distinguished immunophenotypically by the presence of surface immunoglobulins and by reactivity with anti-B cell antibodies. T cells were once characterized by their tendency to form rosettes around sheep red blood cells ("E-rosettes"), but they are now distinguished by detection of a variety of antibodies that have been raised against them. Lymphoid cells that react with neither T cells nor B cells are identified by their reactivity with still other antibodies.

The vast majority of infants and children who have lymphomas with lymphoblastic morphology have T cell lymphomas. However, occasional instances of non-T, non-B lymphomas are seen, particularly in those cases with skin presentation. Almost all patients with differentiated lymphomas, both Burkitt's and non-Burkitt's types, have B cell markers. Most large cell lymphomas are of B cell origin also, although occasional cases have other immunophenotypes.

The distinction between lymphoma and leukemia is often imprecise. In general, leukemia implies the presence of bone marrow involvement; usually the marrow has at least 25% replacement by malignant cells. Four entities are commonly included under the heading of childhood lymphoma: lymphoblastic lymphoma, Burkitt's lymphoma, non-Burkitt and undifferentiated lymphoma, and large cell or histiocytic lymphoma.
TABLE 2
Distribution of Primary Anatomic Sites of Non-Hodgkin’s Lymphoma

<table>
<thead>
<tr>
<th>Site</th>
<th>Totals (%)</th>
</tr>
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<tbody>
<tr>
<td>Abdomen</td>
<td>91 (35%)</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>68 (26%)</td>
</tr>
<tr>
<td>Head and neck*</td>
<td>35 (13%)</td>
</tr>
<tr>
<td>Peripheral nodes</td>
<td>37 (14%)</td>
</tr>
<tr>
<td>Other sites†</td>
<td>31 (12%)</td>
</tr>
</tbody>
</table>

* Includes Waldeyer’s ring, nasal sinuses, cervical and supraclavicular sites.
† Includes bone, epidural area, breast, gonad, orbit, skin and multicentric.

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Any or all of these tumors can invade the bone marrow and, thereby, undergo leukemic transformation. Nonetheless, the clinical behavior of this malignancy (lymphoma/leukemia) is still more likely to approximate that of a lymphoma than to mimic the clinical findings and response to therapy usually seen in childhood leukemias.

CLINICAL PRESENTATION

Non-Hodgkin’s lymphomas in children often present with evidence of generalized disease, although symptoms from involvement of specific lymphoid organs are common (Table 2). Various lymph nodes, including those in Waldeyer’s ring, Peyer’s patches, the thymus, pelvic organs, the liver, and the spleen may be involved. Most lymphomas grow rapidly, and the time of onset from symptoms to diagnosis is usually from a few days to a few weeks. This behavior is in contrast to Hodgkin’s disease, which usually has a prolonged, subacute presentation.

Mediastinal adenopathy usually occurs in association with T cell or lymphoblastic lymphomas. The mediastinal involvement may be asymptomatic if the patient comes to medical attention because of associated cervical or supraclavicular adenopathy or leukemic manifestations. On the other hand, mediastinal adenopathy may present with acute respiratory tract symptoms (Figure 2). Such patients may have pleural effusions or tracheal compression causing pain, tachypnea, cough, wheezing, dyspnea, or respiratory distress. With superior vena caval obstruction, there may be plethora of the neck and face, edema of the upper extremities and face, conjunctivitis, or mental status changes. T cell lymphomas tend to grow rapidly. Thus, if the chest x-ray shows a mediastinal mass, clinical and laboratory studies needed to establish a diagnosis should be done at once and appropriate therapy begun.

Abdominal presentations are seen in approximately one third of patients with non-Hodgkin’s lymphomas. Signs and symptoms associated with abdominal lymphoma may mimic those of appendicitis, with pain, intestinal obstruction, and right lower quadrant tenderness, with or without the presence of fever. These acute findings are due to involvement of the distal ileum, appendix, or cecum by lymphoma. Intussusception may be caused by a lymphoma and may even be reduced by a barium enema. Children with intussusception above the age of 5 years probably should undergo laparotomy to rule out the presence of lymphoma. Other patients may present with massive enlargement of the abdomen due to ovarian, pelvic, or retroperitoneal masses, and ascites (Figure 3). These patients often have signs of a massive tumor burden, such as increased levels of serum uric acid and LDH (lactic dehydrogenase). These children require prompt intervention to prevent uric acid nephropathy and other serious metabolic derangements.

Painless adenopathy may be the presenting symptom for any type of lymphoma. While cervical nodes are most commonly involved, enlargement of supraclavicular, axillary, and inguinal nodes may also be seen. Supraclavicular adenopathy has a particularly high chance of being malignant in origin.
TABLE 3

Diagnostic Studies for Children with Non-Hodgkin’s Lymphomas

1. Examination of malignant cells for histology and cell marker studies
2. Complete blood count
3. Serum uric acid, BUN, creatinine, SGOT, LDH, bilirubin, phosphorus, calcium, and electrolytes
4. Bone marrow examination (aspiration and biopsy)
5. Cerebrospinal fluid examination (cell count, cytology, glucose, protein)
6. Chest x-ray
7. Abdominal ultrasound (may be replaced by CT scan)
8. Computerized tomography of chest and abdomen
9. Bone scan or radiography bone survey

DIAGNOSIS

Non-Hodgkin’s lymphomas cannot be positively identified by the presence of clinical findings alone (Table 3). A biopsy is always required to make the diagnosis. In a patient suspected of having a lymphoma, who has isolated, palpable adenopathy, the choice of a biopsy site is usually obvious. Patients who present with mediastinal involvement, however, may be very poor candidates for surgery due to airway compromise, and alternative sites for tissue sampling should be sought. Such patients often have adenopathy of the cervical or supraclavicular regions, and a biopsy may be obtainable with local anesthesia. Also, many patients with mediastinal lymphoma have involvement of the bone marrow, sometimes with only subtle changes in the peripheral blood. Bone marrow examination should be done before resorting to thoracotomy. Pleural effusions are also common. In these cases, cytologic examination of pleural fluid can be used to make a diagnosis of lymphoma without the need for a tissue biopsy.

Patients with advanced abdominal lymphoma may have ascites. Cytologic examination of ascitic fluid may provide findings useful in diagnosis. As in patients with mediastinal lymphoblastic lymphomas, some patients with advanced undifferentiated lymphomas of the abdomen, either Burkitt’s or non-Burkitt’s, will have bone marrow involvement. In these patients, bone marrow examination may obviate the need for surgical biopsy of the tumor.

Histopathological diagnosis of non-Hodgkin’s lymphoma often requires corroboration with cell-marked studies. Thus, it is important that patients suspected of having a lymphoma be referred to a center with the capability of performing immunophenotyping as well as histologic examination of the tissues. The need for a second biopsy at a referral center may delay therapy and add substantially to morbidity.

A staging work-up should be performed before starting therapy. Imaging studies of the chest and abdomen will determine the extent of disease. A CT scan usually provides the most precise findings, although postero-anterior and lateral chest x-rays and abdominal ultrasound may also be adequate for staging. All patients should have a bone marrow examination. Spinal fluid examination, including a cytocentrifuge prep, is also needed. Levels of serum electrolytes, including creatinine, BUN, uric acid, calcium and phosphate should be determined to look for tumor-induced renal dysfunction. Lactate dehydrogenase (LDH) level may be useful as a correlate of tumor burden.

Unlike the usual work-up for patients with Hodgkin’s disease, a staging laparotomy is not indicated to assess the extent of disease for children with non-Hodgkin’s lymphomas.

The staging scheme most commonly in use for lymphomas in children is that proposed by Murphy at the St. Jude Children’s Research Hospital as outlined in Table 4. Patients with Burkitt’s lymphoma are often staged using the staging system of the National Cancer Institute (NCI) (Table 5). In general, patients with stage I and II disease have localized lymphomas, and have a better prognosis than patients who have tumors located in unfavorable sites or who have advanced and disseminated disease (stages III and IV).

THERAPY

Pre-Chemotherapy Support

One severe complication of both non-Hodgkin’s lymphoma per se and its treatment has been referred to as the tumor lysis syndrome. This complication occurs in patients with disseminated lymphomas, notably the Burkitt’s and lymphoblastic types. The tumor lysis

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syndrome may be present to some extent prior to starting therapy, and may worsen considerably once treatment is started.

As lymphoma cells are destroyed, either by intrinsic cell death or in response to chemotherapy, these cells release various electrolytes and metabolites into the circulation. The most common problem encountered is hyperuricemia. This occurs when nucleic acid purines are catabolized to the relatively insoluble uric acid which may precipitate in the kidney. Hyperphosphatemia may be seen, with resulting renal damage due to calcium precipitates, and secondary hypocalcemia may result in tetany or seizures. If oliguria or anuria results, hyperkalemia may develop. These metabolic derangements may be compounded either by infiltration of the kidneys by tumor or by urinary obstruction due to a tumor mass.

Prevention of the tumor lysis syndrome should be attempted, although this is not always possible. The syndrome should be anticipated in all patients with widespread lymphomas. Administration of allopurinol together with intensive hydration (at least 3 liters of fluids/M²/day) will prevent the adverse effects of rapid tumor lysis in most cases. Alkalization of the urine will increase the solubility of uric acid. However, alkaliphosphatemia occurs, because an alkaline urine promotes precipitation of calcium phosphate. Administration of phosphate binding gels may produce slight lowering of serum phosphate levels. Diuretics may be given to improve urine output, but with caution, because diuretics may rapidly lower the urine pH and may elevate uric acid levels.

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### Table 4

**St. Jude Children's Research Hospital Staging Scheme**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>A single node or anatomic area (except mediastinal or abdominal)</td>
</tr>
<tr>
<td>Stage II</td>
<td>A single extranodal tumor with regional node involvement</td>
</tr>
<tr>
<td></td>
<td>Two or more nodal areas on the same side of the diaphragm</td>
</tr>
<tr>
<td></td>
<td>A primary gastrointestinal tumor, with or without associated mesenteric nodes</td>
</tr>
<tr>
<td>Stage III</td>
<td>Two or more extranodal tumors on both sides of the diaphragm</td>
</tr>
<tr>
<td></td>
<td>Two or more nodal areas on both sides of the diaphragm</td>
</tr>
<tr>
<td></td>
<td>A primary thoracic tumor</td>
</tr>
<tr>
<td></td>
<td>Extensive intra-abdominal disease</td>
</tr>
<tr>
<td></td>
<td>All paraspinal or epidural tumors</td>
</tr>
<tr>
<td>Stage IV</td>
<td>CNS or bone marrow involvement</td>
</tr>
</tbody>
</table>
TABLE 5

NCI Staging Scheme for Burkitt's Lymphoma

| A. | Single extra-abdominal site |
| B. | Multiple extra-abdominal sites |
| C. | Intra-abdominal tumor* |
| D. | Intra-abdominal tumor with multiple extra-abdominal sites |

* All Stage C is applied to cases who have greater than 90% resection of intra-abdominal tumor.

If severe hyperphosphatemia, hyperkalemia, oliguria or urinary obstruction develops, renal dialysis should be instituted at once.

Ideally, time should be allowed to correct metabolic abnormalities resulting from tumor lysis prior to starting treatment. However, the need to delay therapy must be balanced with the concern that some lymphomas have rapid doubling times, and that such a delay may allow time for substantial tumor growth.

SPECIFIC THERAPY

Localized Lymphomas

Current therapy for patients with non-Hodgkin's lymphomas is based on both histologic subtype and stage of the tumor. For the approximately 30% of patients who have localized disease, a number of treatment regimens have provided excellent results, with 80% to 100% long-term disease-free survival.21-25

In many of the earlier successful treatment programs, intensive therapy was continued for two to three years. Because of the excellent results produced by this treatment, more recent studies are seeking ways to reduce therapy for patients with limited disease. A recent trial by the Pediatric Oncology group showed that seven weeks of intensive therapy followed by six months maintenance therapy with 6-mercaptopurine and methotrexate resulted in prolonged disease-free survival in over 90% of cases. The addition of local radiotherapy was deemed unnecessary.26 Also, it was shown that patients who did not have primary tumors in the head and neck did not require CNS prophylaxis.

Disseminated Lymphomas

Therapy for advanced and disseminated lymphomas has not been as successful, although there have been continuing improvements in therapy.

In 1983, Anderson et al.27 observed marked differences in response to therapy between disseminated lymphoblastic lymphomas and non-lymphoblastic

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lymphomas. The latter consisted of Burkitt’s, undifferentiated non-Burkitt’s, histiocytic, and a few other types of lymphoma. Patients with lymphoblastic lymphomas responded best to a ten-drug regimen (a modified LSA2-L2 regimen) (Figure 4). They showed a long-term survival rate of 76%, as compared with a survival rate of only 26% for patients treated with an intensive four-drug regimen (COMP). On the other hand, patients with non-lymphoblastic lymphoma had a 57% survival rate when treated with the four-drug regimen, but had only a 28% survival rate when given the ten-drug regimen.

At present, multidrug regimens, often based on the LSA2-L2 regimen and containing up to 15 agents, are currently being used to treat many children with advanced lymphoblastic lymphoma. However, a much simpler seven-drug regimen has recently been proposed by Dahl et al.28

Advanced non-lymphoblastic disease has not been as successfully treated, although progress has recently been reported. Magrath et al.22 observed a survival rate of 61% in patients with stage III Burkitt’s lymphoma, and Weinstein et al.29 reported a survival rate of 76% in patients with stage III and IV large cell lymphomas. A recent report from Europe showed excellent results for 114 patients with stage III and stage IV non-lymphoblastic lymphoma using an intensive nine-drug regimen.30 These results will need to be confirmed by others.

General Principles of Therapy

Several general principles have emerged in the current treatment of childhood non-Hodgkin’s lymphomas. For localized lymphomas, short therapy (less than one year) is adequate. Also, radiotherapy is not needed and, except for head and neck tumors, CNS prophylaxis may be unnecessary.

Patients with advanced and disseminated lymphoblastic lymphomas require intensive therapy with multi-agent chemotherapy and CNS prophylaxis, consisting of intrathecal chemotherapy, cranial radiotherapy, or both. The total duration of therapy should be two to three years. Local radiotherapy is only needed occasionally.

For patients with advanced non-lymphoblastic lymphomas, intensive therapy for six to 12 months appears to be most successful. CNS prophylaxis is necessary. Radiotherapy is not routinely used.

Until recently, the outcome for patients who relapse while on treatment was exceedingly poor. Current trials in bone marrow transplantation using allogeneic or autologous marrow after intensive chemotherapy offer promise. Significant numbers of these children

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Figure 4. Schema for the LSA2-L2 chemotherapy regimen.
treated with marrow transplantation have shown prolonged survival.31,32

SUMMARY

The non-Hodgkin's lymphomas are a group of diseases for which substantial progress has been made in understanding tumor biology and effectiveness of treatment during the last few years. These advances may provide insight into the development of neoplasms because of recognized association of lymphomas with viral infections and immunodeficiency. The prognosis for patients with non-Hodgkin's lymphomas continues to improve. As a result, current studies on treatment of lymphomas in certain favorable stages have concentrated on reducing the intensity of therapy. For patients with advanced disease, further improvements in treatment are being sought.17

REFERENCES