chapter 71

LYMPHOMAS

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Lymphomas are a result of chromosomal alterations resulting in the uncontrolled growth of cells of lymphoid origin. Among all ages, lymphomas constitute just 4% of all cancers diagnosed annually in the United States.[1] In children, however, this percentage increases to 11%.[2] Combined, Hodgkin's and non-Hodgkin's lymphoma are the second most common childhood solid tumors (behind brain tumors and ahead of neuroblastoma). These two malignancies compose approximately 15% of all childhood solid tumors annually.

Lymphomas have classically been divided into two distinct groups: Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). In 2001, HD was designated Hodgkin's lymphoma (HL) by the World Health Organization (WHO) lymphoma classification system.[3] Typically, patients with both HL and NHL are initially seen with enlarged lymph nodes and may have systemic symptoms of fever and fatigue and/or extralymphatic spread. However, these two types of lymphoma also have clear differences. HL typically is seen as an indolent process, whereas NHL is most often seen in children with a rapid onset of symptoms. Because of this propensity for rapid growth, children with NHL often have associated anatomic and metabolic co-morbidities to such a degree that their recognition and need for treatment constitutes a medical emergency. With HL, treatment is based primarily on staging and less on histologic subtype. In contrast, the current treatment of NHL depends on the histologic and immunophenotypic subtypes in addition to stage.

These two lymphomas are truly a study of contrasts. This is no more evident than in the evolution of their therapy. For years, HL has been one of the most curable cancers. Now, with markedly improved treatment protocols, NHL has a nearly equivalent cure rate.[4] Owing to the historic high survival with HL, its therapy has focused on reduction in intensity. Because of its previously poor prognosis, NHL therapy has focused on intensification of therapy. The use of higher doses of chemotherapy over a short period (as compared with prior methods) has resulted in the dramatic improvement in cure and response of NHL.

Although most histologic types of HL are treated similarly, it is important to classify fully the subtype of NHL because marked differences occur in the effective therapies administered for each type. In considering the surgeon's role in the therapy for childhood lymphomas, there are no real differences between the two types of lymphomas. However, in contrast to other solid tumors of childhood, in which initial resection of the tumor is important, the primary role of the surgeon in the initial management of lymphomas is to ensure the rapid attainment of adequate and properly preserved biopsy material to allow the pathologist the opportunity to make the diagnosis of the specific type and subtype of lymphoma. Except for certain situations, attempts to resect lymphomas at the time of presentation have no role in the modern management of lymphomas.

HODGKIN'S LYMPHOMA

Thomas Hodgkin, in his classic thesis in 1832, described the gross necropsy examinations of seven patients.[5] He noted the association of generalized lymphadenopathy and splenomegaly in six patients without evidence of infection or inflammation. Histologic descriptions of the Reed-Sternberg (RS) cell, the pathognomonic multinucleated giant cell, did not occur until after the turn of the century.[6,7] Even though the etiology was unclear, therapeutic interventions began soon after the discovery of x-rays. More successful application of radiation therapy awaited the description of the disease's propensity for contiguous spread. With this knowledge, application of radiation to the involved and adjacent nodal areas (extended-field technique) resulted in improvements in survival in the late 1930s.[8] In the early 1960s, in acknowledgment of the limitations of the radiologic techniques of that era, the practice of systematic laparotomy, splenectomy, and celiac node and liver biopsy at the time of initial presentation was developed for the purpose of staging and for targeted therapy.[9] This has properly been described as the model for the careful staging of cancer

as a required prerequisite to the design of therapy, which is a hallmark of oncologic practice today.[10,11] During this same time, chemotherapy combinations entered into the physician's armamentarium. With their use, remission and cure rates markedly improved. The improvement has made HL one of the most curable cancers today, with a 5-year survival of 95% for patients diagnosed between 1996 and 2002.[12] With this high expectation for cure, attention over the past decade in pediatric oncology has focused on the reduction of long-term sequelae of treatment. To this end, chemotherapy has evolved from an adjunctive role to a primary one, with the hope of eliminating the need for irradiation (and its attendant sequelae) altogether. When irradiation is needed, if used in combination with chemotherapy, the focus has been to reduce the size of the fields (from extended to involved) and the doses used. The two classic chemotherapy combinations (MOPP: nitrogen mustard, vincristine [Oncovin], procarbazine, prednisone; and ABVD: doxorubicin [Adriamycin], bleomycin, vinblastine, dacarbazine) have evolved to reduce long-term sequelae. Hybrids of these combinations are being utilized to reduce the doses delivered to the patient, with equivalent results and less toxicity.

Incidence and Epidemiology

Among all ages, 7500 individuals each year are diagnosed with HL in the United States, accounting for just 0.5% of all cancers and only 12% of all lymphomas.[1] However, in children, it is the sixth most common type of cancer, with approximately 500 children diagnosed annually.[2] This constitutes 5% of all childhood cases of cancer and 44% of all childhood cases of lymphoma. HL has an incidence of 5 cases/million children age birth to 14 years/year.[13] A bimodal distribution exists when considering all ages, but in children alone a gradual trend is seen of increasing incidence with increasing age (Fig. 71-1). HL is exceedingly rare in children younger than age 2 years and peaks in the adolescent years.[2] Beyond age 11 years, it is the most common of the two types of lymphoma and accounts for about 15% of all cancer in young adults ages 15 to 24 years.[13] A slight male predominance (1.32:1) is noted, but in the youngest children the male-to-female ratio is much larger (12 to 19:1).[2,14]

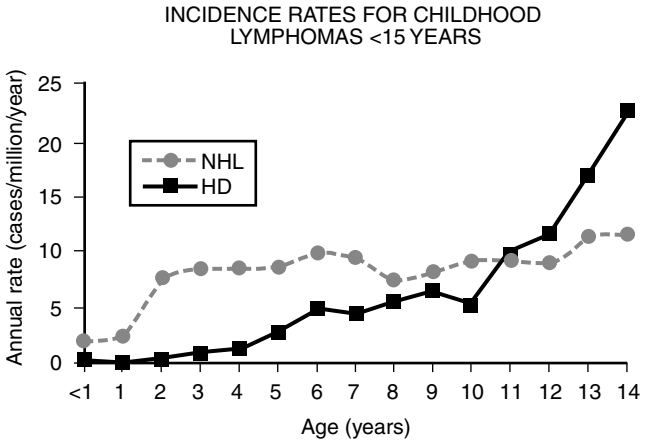

Figure 71-1. Incidence rates for lymphomas in children younger than 15 years. HD, Hodgkin's disease; NHL, non-Hodgkin's lymphoma. (From Gurney JG, Severson RK, Davis S, Robison LL: Incidence of cancer in children in the United States. Cancer 75:2186-2195, 1995.)

HL occurs more often in whites than in blacks (1.3:1).[15] Familial clusters of HL have been noted. Whether this represents risk due to environmental exposure (most often thought to be infectious) or genetics is uncertain. Monozygotic twins of HL patients have been found to be at greater risk of developing HL than are dizygotic twins,[16] strongly implicating genetics as a principal risk factor. Conversely, again in young adults, an increased risk of HL is found with higher socioeconomic status.[17] Young adults with HL come from smaller families, have fewer infectious exposures as young children, and/or have later exposure to infections than do control populations.[17,18] This correlates closely with socioeconomic status and implicates a delayed infectious exposure as a principal risk factor.

Most likely, a combination of genetic risk and infectious exposure predisposes a young adult to HL. Immunodeficiency may be the link between these two risk factors, at least in a subgroup of HL patients. HL is more prevalent in human immunodeficiency virus (HIV)-infected patients.[19-21] Also, patients with HL have a higher incidence of cellular immunodeficiency at the time of diagnosis.[22] Etiologic theories encompass these two risk factors and focus primarily on the Epstein-Barr virus (EBV). Genomic material from EBV has been found in the RS cells in up to 79% of HL cases.[23-25] This has the highest association with the mixed cellularity subtype.[26] An association with EBV is not seen in patients with the nodular lymphocyte-predominant (LP) subtype.[27] A higher risk of HL has been noted in individuals with a history of infectious mononucleosis[28-30] and with previously high titers to EBV.[31] This risk was greater when infected at an older age, and the risk lessened with time from infection.[29] In one report, epidemiologic investigations identified a median incubation time of 4.1 years between infectious mononucleosis and the development of EBV-positive HL.[30] One hypothesis that incorporates these factors suggests the following sequence: (1) a genetic, iatrogenic, or viral immunosuppression; (2) subsequently or coincidentally, an EBV infection or oncogenetic rearrangement in a lymphoid precursor cell; (3) further genetic alterations, followed by (4) clonal expansion of lymphoid cells with morphologic features of RS cells, finally resulting in (5) the clinical syndrome known as HL, diagnosed by the presence of RS cells.[32]

Classification and Histologic Subtyping

The diagnosis of classic HL requires the dual finding of the diagnostic Hodgkin's and RS cells (HRS cells) plus a reactive cellular background.[33] The RS cell is a large cell (15 to 45 mm) with an "owl's eye" appearance

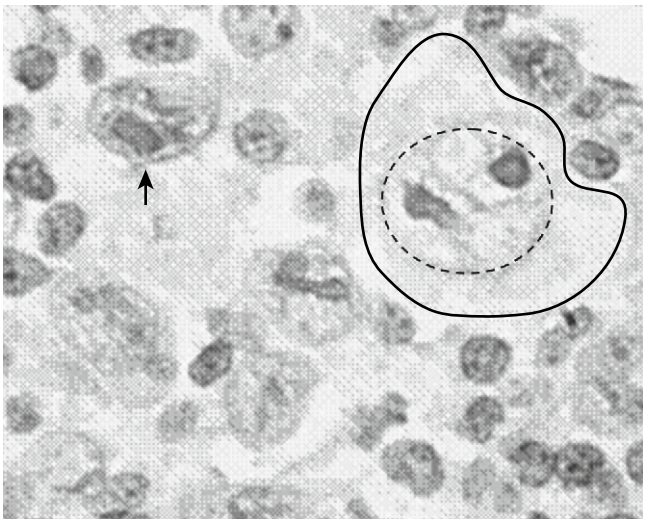

Figure 71-2. This photograph depicts a Reed-Sternberg cell, which is pathognomonic for Hodgkin's disease. On the right side of the slide, the large nucleolus is outlined by the *dotted circle* and the entire cell is outlined by the *solid line.* Note the relatively pale nuclear chromatin. The nucleolus has the appearance of an "owl's eye" from which it receives its name. The *arrow* points to a mononuclear variant of the Reed-Sternberg cell, which has reticulated nuclear chromatin surrounding an almost rectangular macronucleus.

(Fig. 71-2). It has a multilobed nucleus (or is multinucleated), each with a prominent eosinophilic nucleolus surrounded by a clear zone (halo) and an intensely stained nuclear membrane. The "owl's eye" appearance is the result of a bilobed nucleus. The RS cell often makes up no more than 2% of the involved cells. Hodgkin's cells are the mononuclear variant of RS cells. The cellular background is a reactive, pleomorphic mixture of inflammatory cells including reactive lymphocytes, histiocytes, plasma cells, eosinophils, neutrophils, and fibroblasts, with varying degrees of fibrosis and sclerosis. The HRS cell is a clonal, neoplastic cell seen in classic HL and is thought to induce the reactive background through the abundant release of various cytokines.[34] The origin of HRS cells remained elusive until recently because of its paucity in sampled tissue. However, research now indicates that they are usually derived from germinal center B lymphocytes that are clonal and have lost their immunoglobulin gene transcription ability.[35,36] Post–germinal center B-cell origin has been described, as well as a rare case of HL derived from peripheral T cells.[37-41] In classic HL, HRS cells have a unique molecular defect with clonal immunoglobulin gene rearrangement and no immunoglobulin gene transcription or expression. HRS cells typically are CD15 and CD30 positive and negative for CD45 and B-lineage antigens.[42] In contrast, the nodular LP HL cells (popcorn cells) are usually positive for B-lineage antigens, CD15 and CD30 expressions are lacking, and the immunoglobulin genes are expressed.[42]

For histologic typing, the Rye classification was commonly used for 3 decades but has been supplanted by the WHO classification. The 2001 WHO classification lists two main types of HL: classic HL and nodular LP. Classic HL is further divided into four subtypes by morphology. These subtypes include nodular sclerosis (NS, the most common), mixed cellularity (MC), lymphocyte predominant (LPHL), and lymphocyte depleted (LDHL).[3] The NS subtype is seen in 40% of younger patients and 70% of adolescents.[43] It is characterized by tumor nodules surrounded by broad sclerotic bands arising from a thickened fibrotic capsule.[33] This subtype has a strong predilection for involvement of the lower cervical, supraclavicular, and mediastinal lymph nodes. The MC subtype is found in 30% of cases and has an increased incidence in younger children.[14] HRS cells are typically increased in number. The lymph node architecture is often completely effaced by the HRS cells and their surrounding reactive cells. This subtype often is first seen with advanced, widely disseminated disease in extranodal sites. In addition to its relatively common incidence among all HL patients, it is the most common histologic type seen in HIV-infected patients.[21]

From 1978 to 1986, the National Cancer Institute (NCI)-sponsored SEER data revealed the following patient 5-year survival rates using the formerly used Rye classification histologic subtype: LP, 83.9%; NS, 82.2%; MC, 68.1%; and LD, 36.4%.[44] Reports have now shown that LPHL has a better prognosis with markedly reduced therapy needed to achieve cure.[45,46] This differentiation of therapeutic response between LPHL and the other classic HL histologic types appears to validate the distinction observed in the immunophenotyped RS cells.[47] Clinical trials are now underway to explore this difference further and to examine whether reduced therapy for nodular LPHL is possible. The worse outcome of the MC and LDHL types may reflect their typically higher stage at diagnosis.

Clinical Presentation

Children are first seen with painless enlarged lymph nodes, typically in the cervical or supraclavicular nodal groups (Table 71-1). Nodes are often described as rubbery and fixed. They may be either single or matted with other nodes. Occasionally, because of rapid growth, tenderness may be present. Tumor lysis syndrome, a result of rapid and extensive tumor growth and a common complication in children with NHL, is rarely seen in children with HL.

HL tends to spread in a contiguous manner. Therefore, at presentation, one must examine carefully the nodal groups adjacent to the initially identified nodes. More than 90% of patients have involvement of either the cervical or mediastinal nodal groups, or both.[48] Interestingly, HL tends to spread from the cervical nodes of one side of the neck to the mediastinum before it spreads to the contralateral cervical nodes. When surgical laparotomy was included in the staging process (which is no longer routinely recommended), the spleen was noted to be involved in 27% of patients.[48] When evaluating the histologic subtypes and patterns of initial involvement, it is clear from Table 71-1 that the MC and LD subtypes of HL have

Table 71-1 Hodgkin's Disease: Sites of Involvement at the Time of Initial Diagnosis

	Histologic Subtype (%)			
Nodal Sites	*NS*	*MC/LD*	*LP*	*All*
Mediastinum	73	46	8	59
Cervical	55-62	53-60	41-46	55-58
Axillary	11-15	14-16	13-14	13-14
Hilar	14-15	8-9	3-5	11-12
Upper neck	4	4	14	5
Epitrochlear	1	1	6	2
Spleen	24	35	17	27
Upper abdomen	13	18	5	14
Lower abdomen	8	17	8	11
Inguinal	1	3	10	2-3

NS, nodular sclerosis; MC/LD, mixed cellularity/lymphocyte depleted; LP, lymphocyte predominant.

Adapted from Mauch PM, Kalish LA, Kadin M, et al: Patterns of Hodgkin disease: Implications for etiology and pathogenesis. Cancer 71:2062-2071, 1993.

more widespread involvement than do the NS or LP HL subtypes.

Mediastinal disease, in addition to a predilection for certain histologic subtypes, is most common in children older than 12 years, in girls, and in those with constitutional symptoms (also known as B symptoms).[49] Mediastinal disease may appear with significant respiratory compromise due to compression of the trachea, carina, or both, including the major bronchi.[50] These patients may have dyspnea on exertion or at rest, persistent cough, or stridor. They may have recently been treated for presumed asthma or bronchiolitis, without radiographic imaging. Patients with this presentation may have a history of orthopnea and are most comfortable in an upright forward-leaning position to relieve the pressure on the airway (from the anterior mediastinal mass). The physician must be vigilant for mediastinal disease because it may be silent until a patient is sedated for a radiologic or surgical procedure. These patients may prove impossible to aerate even with intubation because of distal tracheal or bronchial obstruction. It is imperative that all patients with suspected lymphoma (HL or NHL) have a chest radiograph or chest CT scan before any sedation or procedure. These patients may also have signs of superior vena caval obstruction, including edema and cyanosis of the face and venous distention. Extralymphatic involvement can include the liver (the most common extralymphatic organ involved), lungs, bone, bone marrow, and skin, among other sites. Whereas bone marrow involvement is present in only 4% to 14% of patients overall, among those patients with stage IV disease it is present 32% of the time.[51]

Most patients have no systemic symptoms at the time of initial diagnosis. About one fourth of patients will have one or more B symptoms, defined as weight loss of more than 10% in the previous 6 months, unexplained recurrent fevers greater than 38°C, or drenching night sweats.[48] Pruritus, fatigue, and anorexia are other nonspecific symptoms seen in HL patients. Laboratory findings in patients at diagnosis are nonspecific and typically are indicative of an inflammatory process. The erythrocyte sedimentation rate (ESR), serum copper, and ferritin levels are frequently elevated and may be monitored later for evidence of relapse. A high ferritin (>142 ng/mL) level or increased ESR (>50) has been associated with a worse prognosis.[52,53] The lactate dehydrogenase (LDH) value may be elevated as well. Although not common, leukopenia may be indicative of bone marrow involvement.[51]

Diagnosis

The diagnostic evaluation should include physical examination and laboratory and radiologic studies (Table 71-2). The physical examination should be directed to the obviously involved nodal groups and also to the adjacent groups, keeping in mind the natural history of HL and its propensity for contiguous spread. The number of involved nodal groups in stage II patients (more than four) has been associated with a worse prognosis and should be carefully determined.[54] The size of the palpable nodal masses should be estimated and recorded. Bulky disease (nodes or nodal aggregates > 10 cm and/or mediastinal tumor width more than one third of intrathoracic width on a posteroanterior chest radiograph or CT) is associated with a worse outcome in low-stage patients and necessitates additional therapy to achieve equivalent outcomes.[55-57] Auscultation of the airway, palpation of the abdomen, and examination of distant nodal groups are critical as well.

Laboratory examination should include full blood cell counts and chemistries, including hepatic function tests, LDH, and ESR. Serum copper and ferritin levels also should be obtained. However, no clinical findings

Table 71-2 Hodgkin's Disease: Diagnostic and Staging Evaluation at Presentation

Complete physical examination with documentation of involved nodal groups (including measurements of nodes), and involved extralymphatic organs
Complete blood cell count, chemistry panel including hepatic function tests, erythrocyte sedimentation rate, copper, ferritin, lactate dehydrogenase
Chest radiography to evaluate for possible mediastinal disease and airway compression
CT scans of areas identified on physical examination (also include chest, neck, and abdomen)
Positron emission tomography
Gallium scan
Bone scan
Excisional biopsy of node
Bone marrow biopsies and aspirates (bilateral)
Lymphangiogram (optional)
Staging laparotomy/laparoscopy (mandatory if considering radiation therapy alone) with splenectomy, nodal sampling, and wedge biopsies of hepatic lobes

are pathognomonic for HL. Ultimately, the diagnosis awaits the biopsy of involved sites, most commonly an excised lymph node. The surgeon's goal is to biopsy the most accessible nodal region to obtain adequate tissue for diagnosis. Open excision of the largest lymph node is preferred because fine-needle aspirations generally do not provide adequate tissue. Excisional biopsy is where the diagnosis is made, based on the pathognomonic finding of HRS cells within a reactive cellular background. For cytogenetic and molecular genetic evaluations, it is imperative that all tissues are placed in a sterile container for fresh samples. Formalin should never be used. For patients critically ill at diagnosis, such as those with severe airway obstruction, diagnosis by alternative methods needs to be considered. These may include nodal biopsy with local anesthesia alone, CT-guided percutaneous needle biopsy of the mass, aspiration of a pleural effusion, or a bone marrow biopsy and aspirate.

Staging

Further evaluation of a patient with HL is required to determine the extent of disease at diagnosis and thus the stage of disease (Table 71-3). The common staging system for HL was adopted in 1971.[58] This system is based on the observation of contiguous nodal spread in HL. Patients are further divided into asymptomatic (A) and symptomatic (B) subcategories. This subclassification for symptomatic patients is based on the findings of a worse prognosis for B patients and the need for a systemic therapy approach in them (i.e., chemotherapy in addition to radiation). This likely reflects the finding that patients with B symptoms are more likely to have distant, widespread disease when pathologically staged.[59]

For HL, the decision for the method and the extent or intensity of therapy rests on the staging results. Traditionally, two types of staging were used in HL patients: clinical and pathologic. Until recently, all patients underwent both methods. Clinical staging includes physical, laboratory, and radiologic evaluations. Pathologic staging requires a staging laparotomy with splenectomy, nodal sampling, and wedge biopsies of both hepatic lobes. The radiologic evaluations have been in evolution over the past decade. Lymphangiograms, once a critical component of staging in HL, have been supplanted by more modern and less invasive imaging modalities. CT examination is used most frequently.[60] For those who will be treated by irradiation alone, accurate assessment of abdominal disease is critical. Staging laparotomy with splenectomy, nodal sampling, and wedge biopsies of both hepatic lobes has been shown to increase the stage of disease in up to 35% of patients initially evaluated with CT[61,62] (i.e., the difference between clinical and pathologic staging). This would seem to indicate that abdominal exporation is important. However, again, with the use of systemic chemotherapy and the de-emphasis on irradiation, this discrepancy between clinical and pathologic staging no longer appears to have a significant impact on treatment or outcome.[63,64]

For the majority of children with HL, staging is based on clinical criteria and laparotomy (or laparoscopy) is not encouraged or recommended. Abdominal staging should continue to be used in patients destined to be treated with irradiation alone (although this is now rare in children) because abdominal disease would have a significant impact on planned therapy.[65] Staging laparotomy (or laparoscopy) with splenectomy is not without its risks. These are the typical postoperative complications of abdominal surgery. Moreover, with splenectomy, there is a lifelong risk of overwhelming sepsis with encapsulated organisms and these patients require lifelong antibiotic prophylaxis.[66] An increased risk of secondary leukemia also exists in those HL patients treated with chemotherapy who have undergone splenectomy (5.9%) compared with those who have not (0.7%) as part of their staging procedure.[67-69]

Nuclear medicine scans are another modality that are increasing in HL patients. Although early studies of gallium scanning found its value suspect,[70,71] it has its greatest impact in identifying unrecognized sites of disease at presentation and in follow-up. This is especially true for patients with mediastinal disease. Patients with NS subtypes will often have persistently enlarged cervical and mediastinal nodes due to scar tissue. Although these are enlarged on CT, negative

Table 71-3 Ann Arbor Staging Classification for Hodgkin's Disease

Stage	Definition
I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I_E)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and its regional lymph node(s) with involvement of one or more lymph node regions on the same side of the diaphragm (II_E)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by involvement of the spleen (III_S) or by localized involvement of an extralymphatic organ or site (III_E) or both (III_{SE})
IV	Disseminated (multifocal) involvement of one or more extralymphatic organs or tissues with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement

Adapted from Carbone PP, Kaplan HS, Husshoff K, et al. Report of the committee on Hodgkin's disease staging classification. Cancer Res 31: 1860-1861, 1971.

gallium scans (in patients in whom these sites were gallium avid at presentation) indicate a non-neoplastic cause (i.e., residual scar tissue).[72,73] It has been suggested that this is most accurately predictive in initially low-stage patients (I or II) and less so in patients with advanced disease (III or IV).[74]

In children, it is important also to recognize the phenomena of thymic rebound after therapy. This may result in both an enlarging mediastinal mass on CT and a positive gallium scan. An experienced radiologist will recognize this phenomenon by its timing (within the first 6 months after therapy has been completed) and by the normal (although enlarged) homogeneous appearance of the thymic tissue. However, false-negative interpretations can occur. Thus, close follow-up of these patients is critical. In the past, shortages of gallium have made this examination more problematic. However, fluorodeoxyglucose-labeled positron emission tomography (FDG-PET) has been found to be more sensitive and specific than either gallium or CT.[75-78] Similar to gallium scanning, it leads to a higher staging in a significant percentage of patients. FDG-PET during and after therapy has been highly predictive of patient outcome[79,80] and helps to differentiate residual scar tissue from residual lymphoma,[81] although false-positive findings with inflammatory conditions have been reported.[80] More experience with this new modality is required before it can be used alone. Finally, the bone marrow examination continues to be important, regardless of planned methods of therapy, because its involvement would upgrade the patient's disease to stage IV status and necessitate more intensive chemotherapy.

Treatment

Principles of Therapy

Several strategies have been effective in the treatment of HL. These have included radiation therapy alone, combinations of irradiation and chemotherapy, and, most recently, chemotherapy without radiation. For children in particular, four principles guide modern HL therapy. For those with early or low-stage HL (I to III), reduction of therapy duration and intensity to reduce long-term sequelae (while maintaining the current high cure rates) is a central principle in today's regimen designs. In concert with this, the reduction and eventual elimination of irradiation as a method of therapy in children with early or low-stage HL is important. The third and most recent principle is response-based therapy. This reduces therapy for those who do not require additional doses by adjusting or eliminating anticipated cycles of chemotherapy based on the tumor's response to the initial courses of therapy. Fourth, for those with advanced-stage HL (stage IV), intensification of therapy and identification of new and more effective regimens to increase relapse-free survival are needed.

Finally, advances in pediatric oncology have been substantial, primarily owing to patients being managed on protocols through the cooperative groups (COG and SIOP). Children, including adolescents, diagnosed with HL should be referred to, and their treatment coordinated through, one of the many centers associated with these groups. These children, through participation in the clinical trials, receive the most advanced and effective therapy available today (Table 71-4).

Principles of Radiation Therapy in the Treatment of Hodgkin's Lymphoma

Despite the goal of eliminating radiation from the therapeutic regimens for children with early-stage HL, it must be recognized that HL is a very radiosensitive neoplasm. A long record of efficacy exists in using radiation either alone or in combination with chemotherapy regimens for this neoplasm. Radiation therapy has traditionally been given to the sites of disease and contiguous, clinically uninvolved, areas. This is known as extended-field irradiation. Various fields of therapy have evolved and include the preauricular (Waldeyer's ring) field, the supradiaphragmatic mantle field (submandibular, submental, cervical, supraclavicular, infraclavicular, axillary, mediastinal, and pulmonary hilar nodal groups), the subdiaphragmatic field (splenic pedicle, spleen, para-aortic nodal groups), and two pelvic fields, inverted-"Y" (common iliac, external iliac, inguinal-femoral nodal groups) or spade (inverted-"Y" excluding those nodes below the common iliac group).

More recently, involved-field irradiation has become more widely used. This is a more attractive option when combined with chemotherapy. In children, involved-field irradiation has been shown to provide excellent local control (97%).[82] A study from Germany identified that not only were the remission rate and disease-free survival no different between involved-field and extended-field irradiation but the side effects (leukopenia, thrombocytopenia, nausea, gastrointestinal toxicity, and pharyngeal toxicity) were significantly reduced when using only involved-field irradiation.[83]

The use of radiation therapy alone remains an option for therapy in adults with low-stage (I to III) HL because it allows them the opportunity to avoid the toxicity associated with chemotherapy.[84-87] Even if relapse occurs in those treated with radiation only, the ability to salvage a long-term cure does not appear to be compromised by delaying the use of chemotherapy until the first relapse.

However, the severe and lifelong side effects of irradiation (cosmetic defects, growth retardation, endocrinologic sequelae, and secondary malignancy) on a growing and developing child are a compelling reason to look for alternative methods. Appreciation for these long-term effects has led to a gradual reduction in the dose and in the size of the field treated. More recently, the focus has been to eliminate irradiation completely in the treatment of children with HL. An adult study suggested that this may be possible for those individuals who achieve a complete

Table 71-4 Therapeutic Regimens for Children with Hodgkin's Disease

Chemotherapy Agents	Stage	Radiation	Radiation Dose	DFS (%)	OS (%)	Reference
None	PSI-IIB	EF	≥3500 cGy	67-82	86-96	84, 85, 86
		IF		41	95	
	CSI-IIB	IF		79-85	96-98	
MOPP	I-II	IF	<2500 cGy	96	100	76, 108
	III-IV			84	78	
	IV	EF	33-4400 cGy	69	78	
COP/ABVD	II	IF	<2000 cGy	96	96	112
	III			97	100	
	IV			85	86	
MOPP/ABVD	I-II	IF	2-4000 cGy	89		105
	III			82		
	IV			62		
MOPP/ABVD	I-III	IF	1500-2500 cGy	100	100	106
	IV			69	85	
MOPP/ABVD	IIB-IV	TNI	2100 cGy	77	91	110
MOPP/ABV	II-IV	IF	3500 cGy	93	90	111
COPP/ABV	I-IV	IF	<2500 cGy	100	100	113
OPPA	I-IIA	IF	3500 cGy	98	100	114
ABVD	III-IV	IF	21-3500 cGy	87	89	109
BEACOPP	II-IV	IF	3-4000 cGy*	87	91	100
Stanford V	I-II	IF	3600 cGy*	97		102
	III-IV			85		

*Radiation given to sites of bulky disease present at diagnosis.

MOPP, Nitrogen mustard, vincristine, prednisone, procarbazine; ABVD, doxorubicin (Adriamycin), bleomycin, vinblastine, DTIC; OPPA, vincristine, prednisone, procarbazine, doxorubicin (Adriamycin) – C, cyclophosphamide; BEACOPP, bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine, procarbazine, prednisone; Stanford V, vinblastine, doxorubicin (Adriamycin)–vincristine, bleomycin, nitrogen mustard, etoposide, prednisone; EF, extended-field irradiation; IF, involved-field irradiation; TNI, total nodal irradiation; cGy, centigray (1 cGy = 1 rad); CR, complete remission; DFS, disease-free survival; OS, overall survival.

response (CR) with four cycles of chemotherapy.[88] The CCG 5942 clinical trial compared no radiation therapy to low-dose (LD) involved-field irradiation in an attempt to eliminate radiation therapy in those patients who achieved a CR after four courses of chemotherapy. Patients who received LD involved-field irradiation had an improved event-free survival (EFS), but overall survival (OS) was not different between the two groups. Currently, combined-modality therapy remains the standard of care for children and adolescents with HL.[89] Trials of patients with stage IA and IIA classic HL and nonbulky disease (low-risk HL) are underway to evaluate whether radiation can be eliminated after three cycles of a more intensively timed chemotherapy regimen.

The small subgroup of children in whom irradiation alone may still be considered for front-line therapy are the fully grown adolescent boys with localized disease (I to IIA). Circumvention of chemotherapy in this particular group avoids the impaired fertility that is a particular concern in boys and is related to the alkylating agents. Also, the adolescent's growth is complete. Therefore, irradiation will not result in permanent cosmetic deformities (i.e., arrest of bone growth). On the other hand, even for this group of boys, new regimens that no longer contain alkylating agents have shown excellent efficacy when used in combination with LD radiation therapy.[90] Because of worries about secondary breast cancer, radiation therapy alone for adolescent girls should be given only after strong consideration for the increased risk of breast cancer known to result from irradiation of the breast tissue at this critical age.[91-95]

Principles of Chemotherapy

Chemotherapy is the therapeutic backbone for children with both early and advanced-stage HL. A large number of chemotherapy combinations have been used for HL. For years, two regimens have been the most widely and effectively used combinations for patients with early-stage HL. MOPP or ABVD is administered over a 12-month period and has resulted in excellent outcomes.[96,97] However, these combinations have proven significant long-term sequelae when administered in full doses for a year. The recognition that successful treatment with chemotherapy for children with HL would have significant impact on their quality of life and ultimate survival has led to newer combinations of chemotherapy. In general, these regimens have been variations of MOPP and ABVD. These hybrids have either replaced those agents having the worst sequelae (e.g., cyclophosphamide for nitrogen mustard) or have involved the originals being given at significantly lower doses, or both.

Newer regimens in low-stage patients are now being examined with lower-dose alkylating agents, which are the causes of the majority of the long-term sequelae seen

in these patients.[90] In addition, the number of cycles or overall duration has been significantly decreased as well.[57,98] Typically, a complete therapeutic protocol currently is given over 3 to 6 months. Radiation therapy sometimes remains a part of these regimens, although it is given at lower doses and encompasses smaller fields. In some studies, the chemotherapy regimens that have been given without irradiation have produced equivalent results to regimens with irradiation in patients with low-stage disease.[99-101] A trial to confirm these early results showed no difference in OS between low-risk patients who received radiation and those who did not.[89] But those patients who were given LD involved-field radiation therapy had a superior EFS. For those with high-risk HL, therapeutic regimens that are intensifying both dose and timing are showing improved outcomes over the traditional regimens, with disease-free survival (DFS) now in excess of 80%.[102-104]

Stage, Histology, and Response-Based Therapy

Until recently, therapy for HL was primarily dictated by the stage at which the child was first seen. Now histology and response to therapy are added to the equation.[45,105] Those with LPHL and low-stage disease may be considered for further reductions in chemotherapy. If the disease is completely resected via an excisional biopsy, no further treatment may be needed. A current clinical trial is attempting to confirm the results of smaller studies showing favorable outcomes with surgical resection alone in stage I patients with LPHL, a single involved lymph node, and a complete resection. Early response to therapy has been shown to identify those with superior cure rates (94% vs. 78% EFS).[105] Many regimens now incorporate this concept into their design, with fewer cycles of chemotherapy or elimination of irradiation for those with early complete responses.

Symptomatic disease at the time of diagnosis calls for therapy similar to that for higher-stage patients. Current recommendations are for patients with stage I to III disease to receive three to eight cycles of chemotherapy, with the number of cycles dependent on the presence of bulky disease (mediastinal or nodal), number of involved nodal sites (in stage II), and achievement of remission after two to four cycles. Those with adverse risk factors receive six to eight cycles of therapy. The decision to use irradiation after chemotherapy remains under study. When irradiation is used, it should be given in low doses (<2500 cGy) and to involved areas only. Male patients with bulky mediastinal disease should receive radiation in addition to systemic chemotherapy, regardless of response to therapy. Attempts are being made to eliminate irradiation in female patients with bulky disease and a rapid response to therapy. Stage IV patients should receive more intensive regimens of systemic chemotherapy and involved-field radiation.

Currently, blood or marrow stem cell transplantation is reserved for those patients whose disease is refractory to systemic chemotherapy or who have experienced relapse. Recent trials have shown that regardless of the duration of initial remission, those who are treated with high-dose chemotherapy and stem cell rescue have less treatment failure than do those treated with conventional chemotherapy.[106]

Results

Most patients treated with combinations of chemotherapy and radiation enter into CR (>90%).[107,108] Many patients, especially those with the NS subtype, may have persistent adenopathy or mediastinal enlargement for months or years after therapy. Although most prove to be cured, close monitoring of these patients is necessary. For those who do not enter remission with today's front-line chemotherapy/irradiation combinations, the prognosis is poor. Therapeutic intensification with subsequent stem cell transplant should be strongly considered.[106,109]

For stage I and II patients, combined-modality (chemotherapy and radiation) therapy typically results in greater than 90% 5-year DFS rates; for stage III patients, greater than 80% 5-year DFS rates; and for stage IV patients, the outcome was until recently greater than 60% (see Table 71-4). This last group has seen significant advances, with successful outcomes now exceeding 80% in several recent trials.[102,103]

Acute Complications

Acute complications of therapy in children with HL are due to either the tumor itself or the therapy. Because of airway compression, anterior mediastinal lymphomas can be a medical emergency. All patients suspected of having a lymphoma should have an immediate chest radiograph or CT scan to determine whether a mediastinal mass is present. Therapy with chemotherapy (preferable in children) or irradiation is effective in the immediate relief of these symptoms. The complications due to splenectomy are due to overwhelming sepsis from encapsulated organisms. This risk is increased because of the myelosuppression and immunocompromising effects of chemotherapy. Fever in the neutropenic patient necessitates hospitalization and intravenous antibiotic therapy. Bone marrow suppression may require transfusions of either red cells or platelets. Specific chemotherapy agents may have immediate complications. These include nausea and vomiting, restrictive pulmonary disease (bleomycin, irradiation), extravasation burns (nitrogen mustard, vincristine, vinblastine, doxorubicin [Adriamycin]), and chemical phlebitis (nitrogen mustard, vinblastine, DTIC). To alleviate these last risks, right atrial catheters are often placed. This also reduces the discomfort of repeated venipuncture required throughout the duration of treatment.

Long-Term Sequelae

The concern over long-term sequelae guides much of modern therapy for HL, both in adults and particularly

in children. These sequelae result from both radiation therapy and chemotherapy.[110,111]

The long-term sequelae of irradiation in growing children are the overriding reason for the efforts to reduce or eliminate it from therapeutic regimens. Bone irradiation may result in shortening of the clavicles in those receiving mantle radiation or a shortened height in those receiving radiation to the spine.[112] Radiation to the neck often results in permanent hypothyroidism[113] and increases the risk of thyroid cancer.[114,115] If radiation is to be given to the pelvis of a female patient, consideration should be given to surgically moving the ovaries away from the field of irradiation.[116]

Second malignancies are a major concern after therapy for HL.[117-119] The most frequent cause of death in long-term survivors of HL is a second malignancy.[120] The relative risk of a second malignancy in HL patients has been estimated to be 5- to 11-fold that of the general population.[118,121] This represents a 15- to 25-year actuarial risk of 7% to 23%.[118,121-123] Second malignancies are more prevalent in those with HL treated before age 21 years than in the older age groups for all tumors except lung cancer.[118] These second cancers include leukemia and solid tumors. The risk of leukemia seems primarily related to the type of chemotherapy used,[121,124] with a cumulative incidence of 3.3%, with a plateau after about 10 years. However, one recent study found a decrease in secondary leukemia among those treated with the newer hybrid regimens.[123] This likely is a result of the reduction in nitrogen mustard and procarbazine (in MOPP) doses, the principal culprits in the development of secondary leukemia.[125,126] Patients treated with ABVD do not have an increased risk of leukemia. The reduction in the incidence of leukemia may be a result of the decreasing use of splenectomy in pathologic staging, because this operation has repeatedly been shown to increase the risk of leukemia in HL patients treated with chemotherapy.[125,127]

Solid tumors, including those of lung, stomach, melanoma, bone, and soft tissue, have accounted for most of the second malignancies, with a cumulative incidence of 13% to 22% at 15 to 25 years. No plateau has been appreciated.[118,121,122] This risk in HL survivors has not decreased when cohorts treated in the 1960s are compared with those in the 1980s.[118] This increased risk of solid tumors is related primarily to irradiation,[128,129] with some added risk when subsequent chemotherapy is used in relapse patients.[130] It has been recognized that radiation exposure to the breast tissue in adult women has resulted in a fourfold increase in rates of subsequent breast cancer,[91-93,131] whereas the risk of subsequent breast cancer is increased by 39-fold if the breasts are irradiated during adolescence.[94] For an adolescent, this increases the probability of developing breast cancer between the ages of 20 and 30 years from 0.04% to 1.6%[95] and may be as high as 35% by age 40 years.[118] For all types of secondary cancer, adolescents seem to be at greater risk than younger children.[115,132] Recent evidence suggests that the risk of breast cancer is slightly reduced by the premature menopause induced by the chemotherapy these patients receive.[133,134] Most patients who received chemotherapy and radiation therapy had menopause before age 41 years, whereas only 9% treated with radiation alone had premature menopause. Menopause before age 36 years had a significant impact on the reduced risk of breast cancer among those receiving radiation. Patients must be closely observed for second malignancies for decades after their therapy has been completed. No plateau in risk has yet been seen.[111,135]

Other long-term sequelae include cardiac complications secondary to mantle irradiation or the use of doxorubicin (Adriamycin in ABVD regimens), or both, that affect up to 13% of patients.[136,137] These complications are typically congestive heart failure due to myocardiopathy and secondary arrhythmias. Occasionally, restrictive pericarditis may occur as a result of radiation. Overall, the relative risk of death due to cardiovascular disease in HL survivors is elevated and especially so in those treated before age 21 years.[111] Pulmonary toxicity due to bleomycin or irradiation, (or both) affected up to 9% of children who received 12 courses of ABVD with 2100-cGy radiation.[138] This high incidence appears to be decreasing with the use of hybrid regimens and low-dose involved-field irradiation.[139]

Infertility and early menopause in women are primarily a result of ovarian dysfunction as a result of exposure of the ovaries to radiation.[140,141] When the ovaries are surgically moved out of the field of irradiation, these problems are less likely to occur.[116,142] Male patients have a 30% to 40% rate of gonadal dysfunction at the time of diagnosis before any therapy.[143] After more than three to six courses of MOPP therapy, all men are usually sterile.[144] This side effect does not follow ABVD therapy.[145] Spermatogenesis is only transiently reduced by pelvic radiation. Although spermatogenesis is significantly affected by the alkylating agents in MOPP therapy, testosterone production seems unimpaired. It is anticipated that with reduction in single and cumulative doses of chemotherapy, with older agents being replaced with less toxic ones, and with the reduction in radiation field size and dose, these long-term sequelae will be further reduced.

NON-HODGKIN'S LYMPHOMA

In contrast to the similarities between adult and pediatric HL, the types of NHL that occur in adults and children, their presentation, their treatment, and their outcome are dramatically different. Most adults with NHL have low- or intermediate-grade lymphomas. In distinct contrast, children with these types of lymphomas are exceedingly rare. Instead, virtually all children with NHL have one of four high-grade, diffuse types: Burkitt's lymphoma (formerly small, non-cleaved cell lymphoma [SNCCL]), precursor T-cell lymphoblastic lymphoma (T-LL), diffuse large B-cell lymphoma (DLBCL), or anaplastic large cell lymphoma (ALCL). Most patients will be seen initially with advanced or disseminated disease (stages III and IV).

These lymphomas typically appear as a rapidly expanding mass with a short symptomatic history. This propensity for rapid growth makes the diagnostic evaluation in a child with suspected NHL a medical urgency, if not emergency. Of all the childhood tumors, NHL has the greatest chance of acute complications at the time of presentation. Anatomic impingement of adjacent structures (mediastinal tumors on the trachea and bronchi, nasopharyngeal tumors on the orbits, bowel obstruction with or without intussusception) and metabolic derangements due to tumor lysis (before and after therapy is initiated) are not infrequent results of its very rapid growth. Better management of the initial anatomic and metabolic complications, improved methods of determining the subtypes of NHL (perhaps the most important reason for improved survival), and better chemotherapy combinations (more intensive, yet shorter) have brought the most dramatic improvements in DFS and OS for children with NHL over the past several decades.[146] Five-year relative survival was 86% for patients diagnosed with NHL from 1996 to 2002.[12] In addition to more intense therapy of shorter duration, the other major change in therapy for children with NHL is the virtual elimination of radiation from treatment regimens. This should reduce the long-term sequelae that would have otherwise resulted. For the surgeon seeing the child with suspected lymphoma, rapid evaluation and proper handling of biopsy material will have dramatic beneficial effects on the outcome for the child.

Incidence and Epidemiology

NHL accounts for 4% of all cancers in adult and pediatric patients, with nearly 53,600 new cases diagnosed annually in the United States.[1] In children, NHL patients accounted for 4.5% of childhood cancers,[12] 8.7% of all solid tumors, and 57% of all lymphomas.[2] The annual incidence is 9.9 cases/million children younger than 15 years/year.[15] Before age 11 years, it is the most common of the two types of lymphoma. A high male-to-female ratio of 3.0 is found, making it the most disproportionately occurring tumor between the two genders during childhood. This large difference is present in all ages of childhood. A 1.4 greater risk occurs in whites than in blacks.[15] This, too, is seen in all ages, with the exception of children younger than 1 year. The age distribution demonstrates two small peaks in incidence from 6 to 7 years and between 12 and 14 years (see Fig. 71-1). The 6- and 7-year olds overwhelmingly have Burkitt's lymphoma, and the teenagers typically have T-LL.

NHL of B-cell origin, either Burkitt's lymphoma or DLBCL, occurs more often in patients with prior EBV exposure, in individuals with a history of immune suppression, and in equatorial Africa.[147-149] Considerable work now convincingly reveals that, in patients with an iatrogenic (e.g., post-transplant, immunosuppressive therapy) or acquired immunodeficiency, congenital-EBV infection has an etiologic role in either the development or the predisposition to B-cell NHL.[150,151] Correlations have been made between viral load levels and the risk of post-transplant lymphoproliferative disorders (PTLDs).[152-154] Patients at greatest risk for PTLDs are those in whom their primary infection with EBV occurs within the first 3 to 4 months after transplantation. For T-LL or ALCL, no such etiologic correlations have been found.

Classification

Over the years, several classification schemes have been used.[155] Among these are the Rappaport, the Kiel, the Lukes-Collins, the WHO, the International Working Formulation, and the Revised European-American Classification of Lymphoid Neoplasms (REAL).[156] REAL was developed as an effort to eliminate the confusion surrounding the diagnosis of the lymphoma subtype caused by the prior variety of classification schemas. The REAL is a consensus classification system based on morphologic, immunologic, and cytogenetic characteristics, in addition to clinical presentation, course, and putative cell of origin.[156]

REAL is the basis for the WHO classification in current use, a comprehensive classification system published in 2001. Childhood NHL primarily consists of just four subtypes in the WHO system: (1) Burkitt's lymphoma/leukemia and Burkitt-like (mature B-cell neoplasms accounting for 39% of NHL patients[4]); (2) T-cell lymphoblastic lymphoma (28%[4]), (3) diffuse large B-cell lymphoma, and (4) mature T-cell neoplasms (ALCL). DLBCL and ALCL were previously lumped together as large cell lymphomas and comprised about one third of the NHL of childhood. With the separation of these two entities, the cases previously identified as large cell lymphoma are now divided almost equally between DLBCL and ALCL.[157] The first two classifications are part of the "small, round, blue cell tumors," which presents the pathologist with the challenge of proper identification. To differentiate these from the other three classic small round blue cell tumors (neuroblastoma, rhabdomyosarcoma, and Ewing's sarcoma) requires the presence of the immunocytochemical marker leukocyte common antigen CD45 (LCA), which is absent on the other tumor cell types.

Burkitt's lymphoma has classically been divided into Burkitt's and non-Burkitt's (Burkitt-like in the REAL classification) subtypes. These are of a mature B-cell origin, with flow cytometric immunophenotyping revealing the presence of surface immunoglobulin IgM, CD10, CD19, CD20, CD22, CD79a, and human leukocyte antigen (HLA)-DR antigens. The histologic appearance of these two types differs in the degree of pleomorphism, with Burkitt's being more uniform appearing than non-Burkitt's. Although a distinction has been made for years between Burkitt's and non-Burkitt's subtypes of diffuse SNCCL lymphomas, no clinical differences are found between these two subtypes.[158] Histologically, the cells of Burkitt's lymphoma are medium sized with round nuclei containing two to five nucleoli, abundant basophilic cytoplasm, and cytoplasmic lipid vacuoles. Owing to its extreme rates of proliferation

and spontaneous cell death, a number of macrophages are seen within this monomorphic field, consuming the dying cells and giving rise to the classic "starry sky" appearance of Burkitt's lymphoma.[156]

Lymphoblastic lymphomas (LL) are distinguished by round or convoluted nuclei, finely dispersed chromatin, inconspicuous nucleoli, and scant cytoplasm. In the vast majority of these tumors, flow cytometry reveals the presence of the T-cell markers CD3 and CD7, with variable positivity for CD2 and CD5. These cells are typically Tdt positive, whereas Burkitt's lymphomas are Tdt negative. This subtype is classified as a precursor T-cell LL in the WHO classification. A small number of LL cases are B-cell precursor and express pre–B-cell antigen profiles.[157]

Large cell lymphomas are a heterogeneous group of neoplasms. Histologically, approximately half are immunoblastic, 40% are large noncleaved cell, and fewer than 5% are large cleaved cell.[159] Flow cytometry shows relatively equal frequencies of B- or T-cell origin (36% and 33%, respectively) with 30% indeterminate.[160,161] A unique subset, identified by the immunophenotype $CD30^+$ (the antigen identified by the Ki-1 monoclonal antibody),[162] is recognized morphologically by its anaplastic characteristics, including very large cells with abundant cytoplasm, atypical lobulated nuclei, and prominent nucleoli. These cells exhibit a cohesive pattern with lymph node sinusoidal invasion. In the WHO classification, this is referred to as anaplastic large cell lymphoma. In the past, this subtype has also been referred to as malignant histiocytosis. The majority (60%) of these children have a T-cell immunophenotype.[160,163] Recent studies reveal that, although it was originally thought to be uncommon in children, it accounts for 40% to 50% of the large cell lymphoma cases.[160,161,164,165]

Cell Biology

Cancer is a result of (1) the inappropriate or unregulated expression of a gene (or both) at either the wrong time in a cell's cycle or in the wrong cell; (2) abnormal combinations of genes producing proteins not normally present in cells; or (3) the loss of gene expression and their products required for cellular control. The first two categories encompass the proto-oncogenes and oncogenes, and the last comprises the tumor suppressor genes. Lymphomas arise from precursors of lymphocytes at various stages of maturation, primarily because of errors in transcriptional factor control and production as a result of proto-oncogenes and oncogenes. Early B and T cells normally splice together different segments of their immunoglobulin and T-cell–receptor (TCR) genes to generate the diverse proteins capable of binding foreign antigens.[166] In lymphoid cancers, this system goes awry because of the inadvertent splicing juxtaposition of TCR genes (proto-oncogenes) to one of these regions. This leads to the abnormal and unregulated expression of this gene (now an oncogene) and the production of its oncoprotein. This oncoprotein eventually leads to the cell's malignant transformation by a variety of mechanisms and, hence, its uncontrolled growth.[166-169] This neoplastic process typically occurs as a result of nonrandom chromosomal translocations or inversions, although deletions and insertions of DNA sequences likely also contribute to the malignant transformation.

Burkitt's lymphoma was the tumor in which this chromosomal translocation process was originally described.[170] The translocation involving chromosomes 8 and 14 was first identified in Burkitt cells in 1976.[171] As a result of this translocation, t(8;14), the *MYCC* oncogene, located on chromosome 8q24, is juxtaposed to the immunoglobulin receptor subunit gene on chromosome 14q32 (immunoglobulin heavy-chain gene). This translocation is found in both African (endemic) and American (sporadic) Burkitt's lymphoma, although the exact breakpoints on chromosome 8 differ.[172] In a smaller percentage of Burkitt's lymphoma patients, *MYCC* is juxtaposed to chromosome 2p11 (κ immunoglobulin light-chain gene), t(2;8), or 22q11 (λ light-chain gene), t(8;22).[173] It is thought that an increased pool of B cells, either through prolonged stimulation (as in the case of malaria) and/or through inhibition of cell death (as in the case of EBV) increases the chance occurrence of these translocations.[174,175] The oncoprotein MYC normally controls progression through G_1 into the S phase of the cell cycle. However, as a result of these translocations, its expression is dysregulated, leading to uncontrolled lymphoproliferation.[176]

Clinical Presentation

By Initial Site of Disease

Overall, unlike those with HL and adult NHL, children with NHL are often initially seen with extranodal disease and typically have disease that spreads by routes other than contiguous nodal pathways. In children, the abdomen is the originating site of disease in 31%; the mediastinum in 27%; and the head and neck in 29%.[4] Other sites include peripheral nodes, bone, and skin. Most abdominal disease primary lesions are due to Burkitt's lymphomas, whereas most mediastinal/intrathoracic primary lesions are due to T-LL (Table 71-5). Disease that occurs primarily in the peripheral nodes and bones is often due to large cell lymphomas, and skin involvement is primarily associated with the $Ki\text{-}1^+$ large cell lymphoma subtype (ALCL).[161,177,178] Correlating with this distribution and the known age peaks of the two types of small cell lymphomas, abdominal primary lesions occur more often in children younger than 10 years, whereas mediastinal primary lesions are more likely to occur in adolescents. Children with abdominal primary lesions may present with nausea, vomiting, abdominal pain, and changes in bowel habits. On physical examination, they may be found to have an abdominal mass in any of the quadrants. Also, they may present with an acute abdomen due to either intussusception (typically due to infiltration of Peyer's patches) (Fig. 71-3) or small bowel obstruction, perforation of an involved bowel wall, or an ileocecal mass mimicking acute appendicitis.[179]

Table 71-5 Non-Hodgkin's Lymphoma: Prevalence of Histologic Subtypes in Primary Sites

	Abdominal	Thoracic	Head/Neck	Peripheral Nodes	Bone	Other*
SNCCL/B cell	74%	4%	48%	17%	6%	29%
LBL/T cell	3%	74%	24%	33%	31%	14%
LCL	23%	22%	28%	50%	56%	57%
Total	100%	100%	100%	100%	100%	100%

*Includes bone.
SNCCL, small noncleaved cell lymphoma; LBL, lymphoblastic lymphoma; LCL, large cell lymphoma.
Adapted from Murphy SB, Fairclough DL, Hutchison RE, Berard CW: Non-Hodgkin's lymphomas of childhood: An analysis of the histology, staging, and response to treatment of 338 cases in a single institution. J Clin Oncol 7:186-193, 1989; and Wollner N, Lane JM, Marcove RC, et al: Primary skeletal non-Hodgkin's lymphomas in the pediatric age group. Med Pediatr Oncol 20:506-513, 1992.

A child older than age 5 years with an intussusception must strongly be considered to have NHL until proven otherwise. Moreover, NHL should always be part of one's differential diagnosis when faced with a 5- to 10-year-old child with an abdominal mass. Radiographic evaluation with either CT or ultrasonography typically reveals a homogeneous mass with or without evidence of central necrosis, arising either from the retroperitoneum or from the bowel wall. Accompanying adenopathy and metastatic dissemination to the liver and spleen is often seen. The bowel loops may simply be shifted away from the mass or may show evidence of intussusception or obstruction (or both).

Children with mediastinal primary lesions may have minimal symptoms, such as a mild cough or audible wheeze, or can have impending airway obstruction. These latter patients may also have significant engorgement of the vasculature in the head, face, and upper thorax because of superior vena cava compression. Thrombosis may be present in these vessels as well. Often these patients will assume a forward-leaning position and cannot tolerate being placed in the supine position because of the anterior mediastinal mass. The patient's history may reveal orthopnea as well as shortness of breath and dyspnea on exertion. The recent onset of asthma symptoms is not uncommon. Shortness of breath also may be due to pleural effusions. A chest radiograph or chest CT scan is an essential component of the patient's initial evaluation before sedation or any procedure (Fig. 71-4). Chest radiography and chest CT will reveal the widened mediastinum

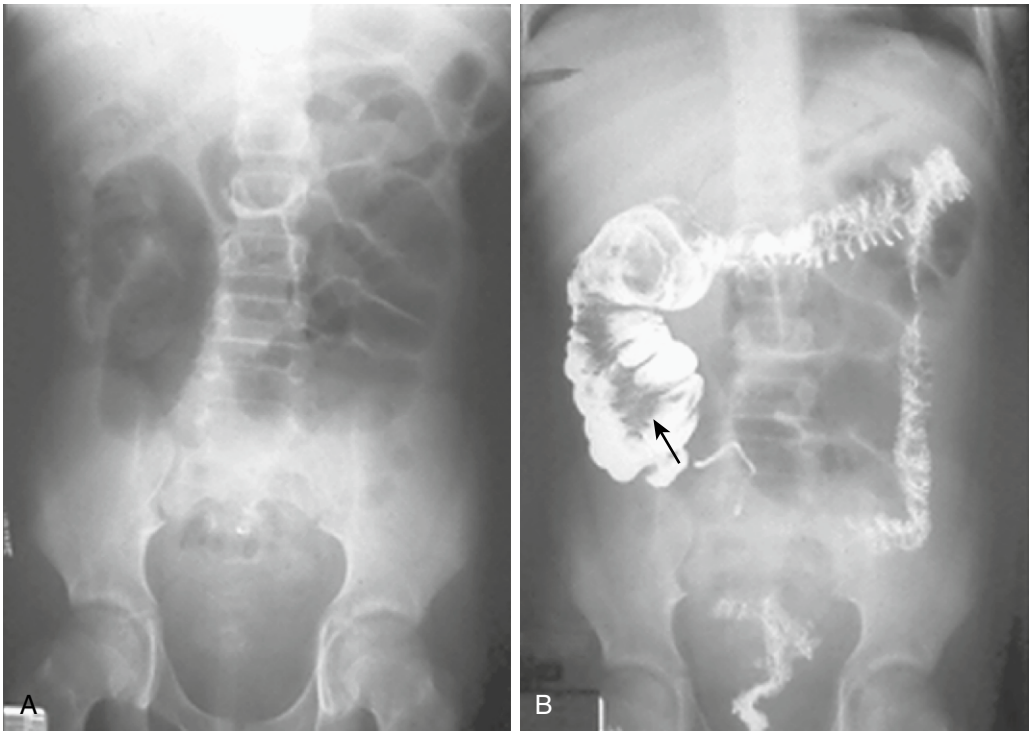

Figure 71-3. This 9-year-old presented with abdominal pain. **A,** The abdominal radiograph shows evidence of a possible small bowel obstruction. Because of the marked leukocytosis and other laboratory parameters, an intussusception due to non-Hodgkin's lymphoma was suspected. **B,** This was confirmed with a retrograde contrast study showing the intussusception (note the filling defect in the contrast medium, *arrow*) in the right colon. This was not able to be reduced radiographically and required operative reduction and intestinal resection.

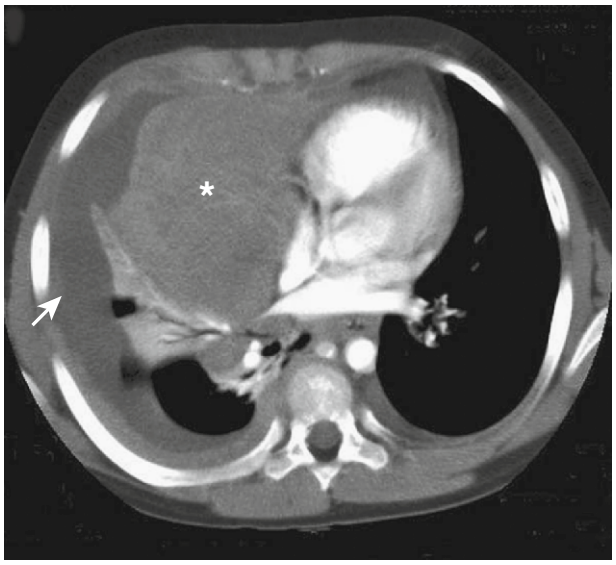

Figure 71-4. This 8-year-old presented with dyspnea. The CT scan shows a very large anterolateral mediastinal mass (*asterisk*). There is also collapse of the adjacent right lung and a rather large pleural effusion (*arrow*). The diagnosis of T cell lymphoma was made on thoracentesis.

with often dramatic narrowing of the trachea and bronchi. Pericardial effusions are often present and may be seen on CT, magnetic resonance imaging(MRI), or echocardiography.[180]

Patients with head and neck lymphomas may have a history of rapidly progressive adenopathy, recent onset of snoring at night, mouth breathing, bad breath, epistaxis, proptosis or periorbital edema, diplopia, extraocular muscle paralysis due to entrapment, cranial nerve paralysis, and sudden blindness or a combination of these symptoms. Physical examination of the nares, oral cavity, and extraocular movements is critical and may reveal signs not appreciated as abnormal by the child. The presence of asymmetric and painless tonsillar hypertrophy should also alert the clinician to the possibility of NHL.[181]

Evaluation with CT often reveals a homogeneous mass that may show destruction of the adjacent bony structures. Bone NHL primary disease is usually seen as lytic lesions found on radiographs obtained for various reasons, including localized tenderness.[182-184] Skin lesions are typically ulcerative and fail to heal but also may be completely subcutaneous.[177] Patients with central nervous system (CNS) involvement may be asymptomatic, have seizures, or have signs and symptoms related to tumor infiltration in the brain.

Laboratory findings at the time of diagnosis are dependent on the amount of tumor present (regardless of the histologic subtype). Generally, patients will have an elevated ESR or C-reactive protein (CRP) level. Those with large tumor burdens typically will have high LDH levels as an indicator of tumor lysis risk,[185,186] disease regression, and disease progression. The degree of LDH elevation has been used as an adverse prognostic factor.[4,187,188] For those with a high tumor burden at presentation, laboratory signs of tumor lysis will also include elevated uric acid, phosphorus, and potassium levels and a low calcium level. Some patients may already be in renal failure at the time of presentation and have an elevated creatinine.[185,186] Hematologic values are nonspecific, and the presence of cytopenias should raise the suspicion of marrow involvement. Cerebrospinal fluid (CSF) pleocytosis may or may not be present in those with CNS involvement.

More than 60% of patients have advanced or disseminated (stages III and IV) disease at diagnosis.[4,189] Bone marrow msetastasis is defined as greater than 5% but less than 25% involvement. Patients with more than 25% disease in the bone marrow are classified as having leukemia. Fourteen percent of patients initially have some bone marrow involvement, and 3% have CNS involvement.[4]

By Histologic Subtype

Burkitt's lymphoma was first described by the surgeon Denis Burkitt in Uganda, where he identified the common finding of enormous involvement of the nodes around the jaw.[190] Later, it was determined that, although this was a common presentation of those patients with endemic Burkitt's (African) lymphoma, those with sporadic Burkitt's (American) lymphoma more typically had presentation of disease either in the abdomen or the nasopharynx.[191] Patients with endemic Burkitt's lymphoma have accompanying abdominal disease in roughly half the cases, and patients with sporadic Burkitt's lymphoma have jaw involvement 15% to 20% of the time.[192] Patients with sporadic Burkitt's lymphoma have a higher incidence of bone marrow involvement (21% vs. 7%) but lower CNS dissemination (11% vs. 17%). Approximately two thirds of Burkitt's lymphoma patients will have disseminated or advanced disease (defined as stages III and IV) at diagnosis.[193]

T-LL patients most often are adolescents with supradiaphragmatic disease, affecting either the intrathoracic region or the head and neck. Disseminated disease is present in nearly 90% of T-LL patients at diagnosis.[193] In T-LL patients, involvement of the bone marrow has been found in approximately one fourth of children, with CNS disease at presentation in fewer than 10%.[193]

ALCL patients may present with disease in all sites but have a higher prevalence than the other two subtypes for skin, bone, and peripheral nodes.[177,184,194] ALCL may present as two distinct clinical forms: primary cutaneous ALCL and primary systemic ALCL (as fevers and weight loss and in advanced stage).[157] Disseminated disease in ALCL patients is present at diagnosis in up to 65% of patients.[193] Involvement of the bone marrow or CNS in ALCL patients is rare (Table 71-6). DLBCL may present as a mediastinal primary lesion or as nodal or extranodal disease, most commonly in the abdomen or head and neck.[157]

In Immunodeficient Patients

For patients with congenital or acquired immunodeficiency, NHL presentation will vary from polyclonal plasmacytic hyperplasia, most often localized in nasopharyngeal nodes or tonsils, to a clonal polymorphic

Table 71-6 Prevalence of Primary Sites among the Three Primary Types of Childhood Non-Hodgkin's Lymphoma

	SNCCL	LBL	LCL
Abdomen	56%	3%	25%
Intrathoracic	2%	65%	21%
Head/neck	34%	23%	29%
Peripheral nodes	2%	7%	11%
Other	5%	3%	14%
Total	100%	100%	100%

NHL, Non-Hodgkin's lymphoma; SNCCL, small noncleaved cell lymphoma; LBL, lymphoblastic lymphoma; LCL, large cell lymphoma.
Adapted from Murphy SB, Fairclough DL, Hutchison RE, Berard CW: Non-Hodgkin's lymphomas of childhood: Analysis of the histology, staging, and response to treatment of 338 cases at a single institution. J Clin Oncol 7:186-193, 1989.

lymphoma slowly arising in the lymph nodes or extranodal sites, to widely disseminated, rapidly progressive immunoblastic lymphoma.[195,196] Symptoms may be nonspecific, with fever and malaise. Hepatosplenomegaly and lymphadenopathy may be presenting signs. Gastrointestinal symptoms of longer than 14 days duration with anorexia, weight loss, and diarrhea should raise suspicion of this condition.[154] NHL has become more common with the use of very potent anti-rejection drugs after solid organ or bone marrow transplantation. Involvement of the transplanted organ is not unusual.[154,197]

Diagnosis

Children initially suspected of having NHL should be evaluated immediately because of the high risk of either metabolic or anatomic complications before therapy begins. The rapid growth of these tumors may create a life-threatening complication overnight in a child who seemed relatively healthy the previous day (Table 71-7).

No clinical findings are pathognomonic for NHL. Ultimately, the diagnosis awaits the biopsy of involved sites, most commonly an excised lymph node or percutaneous needle biopsy. Fine-needle aspirations do not provide enough tissue for the necessary subtyping, which is performed with flow cytometry, molecular genetics, and cytogenetics. It is critical for the excised tissue to be delivered quickly to the pathologist for processing. For cytogenetic and molecular genetic evaluations, it is imperative that all tissue is placed in a sterile container for fresh samples. Formalin should never be used.

For patients critically ill at diagnosis, such as those with severe airway obstruction, diagnosis by alternative methods may be required. These may include nodal biopsy with local anesthetic alone, CT- or US-guided percutaneous needle biopsy of the mass, aspiration of a pleural effusion, or bone marrow biopsy and aspirate. In the majority of cases of NHL, the role of the surgeon is to obtain adequate tissue for diagnosis. Debulking and attempts at local control are unnecessary (with one exception) because NHL is a systemic disease that requires chemotherapy. The one instance in NHL patients in which initial total resection may be considered are those patients with an abdominal mass in whom bowel resection is already required because of perforation or obstruction. In this case, total resection of the tumor should be considered. In this setting, resection reduces the stage of the patient's disease, improves survival, and reduces the amount of therapy required.[198] For all other patients, resection of the mass provides no improvement in staging or long-term cure and delays the time to initiation of chemotherapy. It should be remembered that most patients have disseminated disease at presentation. Also, it is important to note that with chemotherapy alone, more than 90% will achieve a complete remission.

Once NHL is suspected, a concerted and well-conceived plan of evaluation is important to achieve a diagnosis as quickly as possible. This should include laboratory examination to evaluate tumor burden and presence or risk of tumor lysis syndrome. The radiographic evaluation in these patients is extremely important.[60] No procedures or sedation should be attempted until a mediastinal mass has been excluded. To identify the extent of disease, CTs of the neck, chest, abdomen, and pelvis are required. An examination of the head, either CT or MRI, should be obtained in those patients with CNS symptoms, with CSF pleocytosis, or in whom the primary lesions are parameningeal based. Bone scans should typically be obtained. ^{18}FDG-PET or gallium scans are currently recommended. Gallium scans are an effective method for assessing the extent of disease at initial diagnosis, to evaluate residual disease at the end of therapy, and for ongoing monitoring for relapse after therapy.[199] A positive gallium scan at the end of therapy is a strong predictor of relapse. ^{18}FDG-PET scans are gradually replacing gallium scans in the diagnostic evaluation and monitoring of NHL

Table 71-7 Non-Hodgkin's Lymphoma: Diagnostic and Staging Evaluation at Presentation

- Complete physical examination with documentation of involved nodal groups (including measurements of nodes) and involved extralymphatic organs
- Complete blood cell count, chemistry panel (including hepatic and renal function tests), erythrocyte sedimentation rate, lactate dehydrogenase
- Chest radiography to evaluate for mediastinal disease and airway compression
- CT scans of areas identified on physical examination (also include chest, neck, and abdomen)
- Bone scan
- Gallium scan
- Excisional biopsy of node or mass with samples sent for routine pathology, molecular genetics, cytogenetics, and flow cytometry
- Bone marrow biopsies and aspirates (bilateral)
- Lumbar puncture with CSF analysis of cytocentrifuged sample

CT, computed tomography; CSF, cerebrospinal fluid.

patients. Advantages of PET over gallium include same-day imaging, improved resolution, and a higher target-to-background ratio.[200] Diagnostic PET scans are reliable (greater than 90% positive) in patients with DLBCL. Three studies of patients with HL and NHL found PET to be superior to gallium for diagnosing disease sites.[80]

Pathologic evaluation of the biopsy material should include general histochemical techniques to confirm the lymphoma and its subtype. Critical additions to the basic evaluation are flow cytometric analysis of cell-surface markers to determine the immunophenotype of the lymphoma, cytogenetic evaluation for diagnostic translocations, fluorescent in situ hybridization (FISH), and DNA analysis using either Southern blotting or the polymerase chain reaction for detection of the pathognomonic oncogenes (gene rearrangements), even in the absence of identifiable cytogenetic translocations.[201] Examination of markers in tumor cells for EBV is important in the evaluation of PTLDs. These are all essential components at the time of initial diagnosis and should be performed at an institution capable of performing all of them. Therapy differences between the subtypes of lymphoma are such that assignment to the wrong subtype due to a lack of adequate diagnostic material will adversely affect the chance of cure. These evaluations may be performed with biopsy material from any involved site, including the primary mass, enlarged lymph nodes, effusions, and bone marrow. A new technique, known as gene expression profiling, which uses DNA microarrays, has been shown to categorize patients further into specific histologic and genetic subsets of lymphoma, with much greater predictability of the clinical outcome.[202] This new technique will likely revolutionize diagnostic and prognostic characterization for NHL.

Completing the diagnostic protocol is the determination of whether or not there is CNS or bone marrow dissemination. Lumbar puncture for cytocentrifuged CSF analysis should be performed in all patients. However, in those with localized abdominal Burkitt's lymphoma, and those with large cell lymphoma, the benefit gained from this is arguable because of the low incidence of CNS disease in these subpopulations. Bone marrow evaluation should include bilateral iliac crest biopsies and aspirates.

Staging

Once the diagnosis of NHL has been made, staging permits determination of the extent of disease at presentation. This provides direction in monitoring disease response to therapy. In contrast to HL, relapse does not necessarily occur at the site of initial or previous disease in NHL. Thus, this initial staging should not limit the extent of monitoring for relapse after therapy is completed.

Staging is important in the determination of therapeutic planning. The most widely used staging schema today is the St. Jude's or Murphy system (Table 71-8).[203] This is an adaptation of the Ann Arbor scheme and is applicable to all types of childhood NHL. It divides patients into localized (stage I or II) and disseminated or advanced (stage III or IV) disease. Involvement of the CNS or bone marrow immediately places the patient in the stage IV category. Patients with more than 25% bone marrow involvement are, by definition, diagnosed with leukemia rather than with lymphoma. These would include B-cell or Burkitt's leukemia (L3 leukemia morphologic classification) and T-cell leukemia. The former patients are treated on B-cell NHL protocols with much better results than previously obtained on acute lymphoblastic leukemia (ALL) regimens. Many of the B-cell NHL protocol results reported in the literature include these patients in their stage IV populations. The T-cell leukemia patients remain on ALL protocols, but many similarities exist between these protocols and those used in T-LL therapy.

Table 71-8 St. Jude's (Murphy) Staging System for Childhood Non-Hodgkin's Lymphoma

Stage	Definition
I	Single tumor (extranodal) or single anatomic area (nodal), excluding mediastinum or abdomen
II	Single tumor (extranodal) with regional node involvement On same side of diaphragm: a) Two or more nodal areas b) Two single (extranodal) tumors with or without regional node involvement Primary gastrointestinal tract tumor (usually ileocecal) with or without associated mesenteric node involvement, grossly completely resected
III	On both sides of diaphragm: a) Two single tumors (extranodal) b) Two or more nodal areas 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%)

CNS, central nervous system.

Prognostic Risk Factors

When all patients are treated similarly, the stage of the lymphoma at diagnosis is a strong predictor of outcome.[4] Prediction of a patient's eventual outcome stratifies patients at high risk for relapse to more intensive or novel therapies and patients at low risk to shorter, more moderate therapies. Many prognostic factors have been evaluated over the years. All prognostic factors are dependent on the therapy subsequently given.[4] It has been definitively shown that histology-based therapy is of critical importance in the successful outcome of patients (Table 71-9).[189]

CNS involvement in both SNCCL and LBL patients has predictably worse outcomes.[189] In patients with Burkitt's lymphoma, the adverse effect of CNS disease

on outcome has, in some studies, been more attributable to tumor burden at diagnosis than to the presence of CNS disease alone (i.e., those with greater tumor burden are more likely to have CNS disease).[204] Patients with Burkitt's lymphoma older than 15 years of age have a worse prognosis than patients younger than 15 years old. An LDH greater than 500 IU/L also predicts a worse outcome for patients with Burkitt's lymphoma.[205]

DLBCL and ALCL patients (historically large cell lymphoma patients) have unique prognostic characteristics that are likely to change as this entity is better described and therapy is more appropriately administered by subtype. Skin involvement at presentation in patients with large cell lymphoma has been shown to be a poor prognostic indicator.[198] In one study of patients with advanced large cell lymphoma, the presence of $CD30^+$ cells indicated a better OS.[206] However, in another study, no effect on prognosis was noted.[160] B-cell immunophenotype has been shown to improve prognosis.[160] Patients with intrathoracic primary lesions have a better prognosis than do those with primary lesions elsewhere.[206] Children with NHL arising in the bone, regardless of the histologic subtypes, have an excellent prognosis with histology-directed chemotherapy alone.[207]

Table 71-9 Selected Therapeutic Trials for Children with Non-Hodgkin's Lymphoma

Protocol/Therapy	Stage	DFS % (yr)	OS % (yr)	Reference
Small Noncleaved/B cell				
POG/ADCOMP	I-II	87 (4)	93 (5)	217
CCG 551, 501/COMP	I-II	86-98 (5)	91-98 (5)	210
CCG 551/COMP	III-IV	50 (5)	54 (5)	193
CCG 551/LSA_2L_2	III-IV	29 (5)	33 (5)	193
CCG 552/CHOP	III, LDH < 500	86 (4)	86	191
	III, LDH > 500	39	39	
	IV	38	48	
Total therapy B	III	86 (2)		226
POG/Intensified total therapy B	IV	79 (4)		212
HiC-COM	III	92 (3)		192
	IV	50		
SFOP/LMB 84	III	80 (3)	82 (3)	211
	IV	68	71	
SFOP/LMB 89	I-II	100 (1)		226
	III	89		
	IV	80		
Lymphoblastic/T cell				
POG/ADCOMP	I-II	87 (4)	93 (5)	217
CCG 551/LSA_2L_2	III-IV	64 (5)	67 (5)	193
CCG 551/COMP	III-IV	34 (5)	45 (5)	193
CCG 552/CHOP	III-IV	54 (4)	77 (4)	191
CCG 502/ADCOMP or LSA_2L_2	Localized	84 (5)		214
	Disseminated	67		
UCCSG 8503	Disseminated	65 (4)		226
St. Jude/Total therapy X-high risk	III-IV	73 (4)		226
SFOP/LMT 81	III	79		226
	IV	72		
Large Cell				
St. Jude/CHOP	I-II CD30+	75 (5)		161
	I-II CD30-	92		
St. Jude/CHOP & MACOP-B	III-IV CD30+	57	84 (5)	
	III-IV CD30-	29	27	
CCG 551/LSA_2L_2	III-IV	43 (5)	44 (5)	193
CCG 551/COMP	III-IV	52 (5)	69 (5)	193
BFM 83,86,90	I	75 (5)		165
	II	68		
	III-IV	86		
POG 87191/POG 8615	B cell/ALL	96 (3)		160
	T cell or?/ALL	67		
	B cell/III-IV	100		
	T cell or?/III-IV	69		

DFS, disease-free survival; OS, overall survival; LDH, lactate dehydrogenase.

Treatment

Therapy for childhood NHL has evolved over the past several decades, and is based on the knowledge that this tumor is extremely chemosensitive. For Burkitt's lymphoma and large cell lymphoma, the duration of therapy has become shorter, as it became apparent that most, if not all, patients were experiencing relapse within the first 6 to 8 months of therapy.[193,208] Despite reduction in therapy to 6 months or less, no increase in relapse has been seen. Relapses for the most part have occurred within the first 6 to 8 months after diagnosis and virtually all have occurred within the first 2 years.[187-189,208,209] Therapy for Burkitt's lymphoma has shown a clear improvement as methotrexate and cytarabine doses have been increased. These two agents, in addition to cyclophosphamide, vincristine, doxorubicin (Adriamycin), and prednisone (and etoposide for the stage IV patients), now play a critical role in the successful outcome of these children.[193,198,209,210] The addition of rituximab (an anti-CD20 monoclonal antibody) and rasburicase (a recombinant urate oxidase for treatment of hyperuricemia) is currently being studied.

For T-LL, the duration of therapy has been decreased to 2 years. The most effective regimens for LBL have been ones similar to the intensive T-cell ALL protocols in current use. For ALCL patients, the use of T-cell regimens without much CNS-directed therapy has been efficacious.

For Burkitt's and large cell lymphomas, it has become apparent that no benefit in DFS or OS is gained with the use of radiation for treatment, either to involved areas or to the CNS for prophylaxis.[164,177,211] Rather, prophylaxis to prevent CNS relapse is effectively accomplished with intrathecal chemotherapy.[204] Although some type of CNS prophylaxis is thought to be needed for all patients with NHL to prevent CNS relapse, in one small group of patients, it is not. Patients with localized, resected gastrointestinal primary tumors with Burkitt's or large cell lymphomas do not have CNS relapse, even in the absence of CNS prophylaxis.[208]

For patients with LBL, irradiation to areas of bulky disease has been eliminated. In the past, irradiation was used for CNS prophylaxis in patients without CNS disease at diagnosis, but recent studies substituting intrathecal chemoprophylaxis have not shown increased CNS relapses. For those patients with LBL with CNS disease at diagnosis, irradiation remains an important part of their therapy.

Several additional points deserve mention. The use of corticosteroids before a diagnostic procedure should absolutely be avoided. This can induce rapid necrosis in the lymphoma, making subtype determination difficult if not impossible, and potentially jeopardizing the patient's outcome. However, once adequate tissue has been obtained, chemotherapy including corticosteroids is an excellent method for rapid reduction of a life-threatening mass. Because of the extreme sensitivity of NHL, one can anticipate rapid reduction of tumor size once therapy is initiated. Radiation therapy is not necessary. It is not unusual to have symptoms completely resolve within 24 hours and have patients be in complete radiographic remission within 7 days. Many protocols now call for a period of reduced-dose chemotherapy for the first week to obtain a more controlled tumor reduction because of the severe tumor lysis that may accompany more rapid, therapy-induced necrosis.

NHL in immunodeficient individuals is most often a B-cell lymphoma, either small or large cell. Therapy for these patients has typically been directed toward these histologic types. For patients with ongoing iatrogenic immune suppression, a reduction of the immunosuppressive agent with or without acyclovir may be adequate to induce a remission in up to 75% of cases.[154,212] However, this may not be possible after transplant because of the risk of rejection. Interferon-alfa has been used with mixed success in these patients and may exacerbate rejection. A small proportion of patients with localized disease may be cured with operative resection of the involved nodal tissue. When the tumor is resistant to these approaches, chemotherapy regimens can be used, although mortality has been higher than that found in immunocompetent patients. In the past few years, new methods using monoclonal antibody therapy, primarily rituximab, have been used with promising results alone, but these antibodies are most efficacious when combined with chemotherapy.[213]

Results

When reviewing the outcomes of children treated for NHL, it is quickly apparent that considerable improvement in DFS and OS has occurred over the past several decades (see Table 71-9).[4] Today, typically 90% to 100% of patients will achieve complete remission.[164,208,214] Five-year relative survival rates for children ages birth to 19, diagnosed between 1996 and 2004, were 83.3%.[13] Patients with localized disease have an overall excellent prognosis, regardless of histologic subtype, with DFS typically exceeding 90% to 95%. Burkitt's lymphoma patients with advanced disease have experienced DFS exceeding 80% in the recent trials. Patients with LBL with disseminated disease are not faring as well, but DFS for these patients is exceeding 65% to 70% in most trials. Overall, when they occur, treatment failures typically happen within the first 2 years after diagnosis. Patients with Burkitt's lymphoma who experience relapse primarily do so within the first 6 to 8 months. LBL patients will have an occasional late failure after 2 years, although even in this group of patients the vast majority of failures will occur early.[214] Patients with large cell lymphoma have more late relapses. Thus, radiographic follow-up is an important modality in the ongoing post-therapeutic evaluation of NHL patients for several years. With the advent of modern radiographic techniques, second-look operations have not been beneficial to patient outcome.[198,215]

Acute Complications

Depending on the tumor burden at diagnosis, patients may initially have a constellation of significant metabolic derangements known as tumor lysis

syndrome.[185,186] This includes hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia. Recognition of this syndrome is critical to prevent life-threatening complications, including acute renal failure. Without treatment, the incidence of acute renal failure may be as high as 30%.[216] Tumor lysis syndrome is the result of the rapid turnover of cells within the tumor. The fraction of tumor cells in S phase at any given time can approach 27% in some patients.[217] These tumors have a high degree of spontaneous lysis at the time of diagnosis because they rapidly outgrow their blood supply. Any manipulation, including transfusion or operation, may induce a sudden worsening of this syndrome.

Therapy is primarily based on the risk of developing hyperuricemia. For those at high risk, determined by the presence of an elevated LDH, creatinine, or uric acid value, intervention is important. For most patients with little or no elevation in these values, adequate hydration (>3000 mL/m^2/day) and monitoring of blood pH (maintain between 7.0 and 7.5) is adequate, along with the initiation of allopurinol to reduce the production of uric acid through inhibition of xanthine oxidase.[218] Rasburicase, which cleaves uric acid into allantoin, a soluble by-product, has been approved for use by the U.S. Food and Drug Administration (FDA). This agent, administered daily for 1 to 5 days, dramatically reduces measurable uric acid levels to immeasurable levels, thus allowing the clinician to focus on prevention or treatment of hyperphosphatemia, which requires maintaining acidic urine.[219,220] Despite these measures, it may be necessary to place patients on dialysis either to treat oliguria/anuria or to prevent it in the presence of rapidly increasing uric acid, phosphorus (typically >10 mg/dL), or potassium (>7.5 mEq/L) levels.[193,221] In an effort to avoid this complication, some regimens have used an initial low-dose therapy (usually 1 week) to more slowly reduce the tumor burden.

Because of the much more myelosuppressive regimens required in NHL therapy, infection is a much larger risk for NHL patients as compared with HL patients.[189] In one recent study, 63% of the deaths were due to infection. Most patients require transfusion support during treatment because of the myelosuppression. The chemotherapy itself may cause acute complications, including severe chemical burns due to extravasation of certain vesicant agents (vincristine, anthracyclines). Because most children require the placement of right atrial catheters to facilitate their therapy, thrombosis of this area and the surrounding vasculature has become more frequent.[222] Mucositis is seen in a significant number of patients during therapy for Burkitt's lymphoma as well.

Long-Term Sequelae

As long-term survival has improved, the concern over lifelong sequelae has increased in these patients. With current therapy, these complications include cardiac toxicity,[137] infertility as a result of the alkylating agents used,[223] and secondary leukemias due to epipodophyllotoxins (etoposide, tenoposide) and alkylating agents used in the NHL regimens.[224] The risk for developing cardiac toxicity is related to several factors, including irradiation dose, cumulative anthracycline dose, and age at exposure. Patients are at an increased risk for anthracycline-related cardiomyopathy if they are female, have received doses greater than 200 to 300 mg/m^2, and were younger when given anthracyclines.[225]

The risk for infertility is related to the cumulative dose of the alkylating agents. Fertility is likely to be maintained in males receiving less than 4 g/m^2 of cyclophosphamide and no other alkylating chemotherapy or radiation.[225] In female survivors, the risk of infertility increases with age at the time of treatment. Prepubertal patients tolerate higher cumulative doses of alkylating agents than adult women. Survivors of childhood lymphoma must be monitored closely for early identification and proper intervention to maintain a good quality of life in these long-term survivors.