Classification, Staging and End Results of Treatment of Childhood Non-Hodgkin's Lymphomas: Dissimilarities From Lymphomas in Adults

Sharon B. Murphy

THERE ARE MANY FACTORS responsible for variations in the clinical manifestations of disease between adults and children, even assuming the disease in question has an identical etiology at all age levels. These differences are implied in the aphorism that the child is not a miniature adult, and they include variations in anatomic, physiologic, pathologic and immunologic patterns. Considering the lymphoid system, the newborn enters life with a small amount of lymphoid tissue and total naivete, his only host defense consisting of passively transferred maternal antibody. The amount of lymphoid tissue increases rapidly during early childhood, reaches adult size by 6 yr and exceeds adult size from that time until puberty, when atrophy begins. The actual number of lymph nodes increases threefold in the same period.[1] It is characteristic of infancy and childhood that lymph glands are prone to swelling and hyperplasia. In fact, cervical lymph nodes are universally palpable in children. In his authoritative pediatric treatise of 1899, Holt used the term "lymphatism" to refer to this diathesis, "the exaggerated susceptibility of lymphoid tissue in childhood to respond to any inflammation by hyperplasia, which may be out of proportion to the exciting cause and which continues after the cause has ceased to operate."[2] The differential diagnosis of lymphadenopathy that may simulate lymphoma in children is therefore not a trivial problem,[3] but one which is beyond the scope of this review.

This review will consider the characteristics of childhood non-Hodgkin's lymphomas (NHL), highlighting natural history, management, and end results, emphasizing dissimilarities from lymphomas occurring in adult years. Childhood will arbitrarily be defined as the period from infancy to adulthood, encompassing adolescence, roughly up until the fifteenth to eighteenth years of life. The lymphomas typical of childhood naturally do not vanish at an arbitrary upper threshold in maturity but rather decline in frequency. A separate emphasis on childhood NHL is warranted for numerous reasons, not the least being that a better insight into ontogeny may be gained. Children experience a different spectrum of malignant disease than adults do, the common sites of origin typically being embryonal tissues of the hematopoietic system, central and sympathetic nervous system (including the eye and the adrenal), soft tissue, bone and kidney, in contrast to the common adult tumors of differentiated epithelial tissue, like skin, lung, and alimentary tract. Presumably genetic mechanisms must be operating to explain to some degree the earlier onset of tumors in childhood, without the intervening cumulative life experience with environmental carcinogens.

EPIDEMIOLOGY

Lymphomas are the third most common neoplasm affecting U.S. white children, and approximately 60% of these are non-Hodgkin's.[4] The most common neoplasm in childhood is acute lymphoblastic leukemia (ALL), and the lymphoma-leukemia complex is apparently linked by an increasingly recognized series of common factors. Histologically and cytologically their distinction may be difficult, though clinical presentation remains the basic guide to their conventional separation. Substantial differences in the ratio of the frequencies of childhood lymphomas and leukemias are observed in other parts of the world, such as the Middle East, Nigeria, and Uganda.[5,6] In these areas, lymphomas are the most common cancers encountered in children, leukemias being relatively deficient and in low prevalence.

The peak frequency of ALL is between the ages of 2 and 4 yr, whereas the peak frequency of

From the Division of Hematology and Oncology, St. Jude Children's Research Hospital, Memphis, Tenn.

Supported in part by the Cancer Center Support (Core) Grant CA21765 from the National Cancer Institute, and by ALSAC.

Address reprint requests to Dr. Sharon B. Murphy, 332 North Lauderdale, Memphis, Tenn. 38101.

© 1980 by Grune & Stratton, Inc.

0093–7754/80/0703–0010$02.00/0

NHL cases in most reported series of children is between 7 and 11 yr, the median being 9. The frequency of ALL, as well as the excellent response to therapy, diminish with advancing years. The frequency of NHL increases with age, and the proportion of affected women more closely approximates men.[7] In childhood NHL, there exists a marked male predominance, 3:1. The explanation for the unequal gender distribution of lymphomas in childhood remains obscure, though the sex-linked recessive syndrome of lymphoproliferative disease reported by Purtilo provides a clue.[8]

CLASSIFICATION AND FUNCTIONAL CHARACTERIZATION OF TUMOR TYPES

In childhood, the histologic pattern of lymphomas is limited essentially to one of three diffuse types: lymphoblastic, undifferentiated, or so-called "histiocytic" or large lymphoid cell (Table 1) with a small proportion of cases ordinarily unclassifiable.[9-12] Lymphoblastic lymphomas constitute at least a third of all childhood lymphomas and are composed of immature lymphoid cells indistinguishable from the lymphoblasts of ALL. Fine morphological subclassification, based on presence or absence of convoluted tumor cell nuclei, is of no clinical relevance.[13] The designation "undifferentiated" to refer to the next most common category of childhood lymphomas is admittedly arbitrary but conventional in keeping with Rappaport's modified classification and the original WHO definition of Burkitt's lymphoma. It is recognized however that later it was shown that Burkitt's lymphoma is not undifferentiated, but rather a B-cell lymphoma of probable follicular center cell origin. The so-called "histiocytic" or large lymphoid cell category is morphologically and immunologically heterogenous, and the morphological distinctions between large noncleaved follicular center cell and immunoblastic or pleomorphic pyroninophilic tumors are not always clearcut. It is furthermore not clear but unlikely that such morphological distinctions constitute meaningful differences in clinical behavior or treatment planning in children. The author is aware of no published evidence pertaining to childhood purporting to show that pleomorphic or immunoblastic, large lymphoid, non-Burkitt, but B-cell (surface-immunoglobulin positive) tumors, differ significantly in their clinical behavior from nonendemic Burkitt's lymphoma, strictly defined on the basis of cytologic uniformity.

Table 1. Distribution of Histopathologic Types of Diffuse Lymphomas Typical of Childhood

Histologic Classification	Approximate Frequency (%)
Lymphoblastic	30–50
Convoluted	
Nonconvoluted	
Undifferentiated	20–40
Burkitt	
Non-Burkitt, pleomorphic	
"Histiocytic," large lymphoid cell	15–20
Unclassifiable	5–10
Total	100

While all childhood lymphomas exhibit a propensity for extra nodal involvement and early wide noncontiguous dissemination, there is a definite relationship between the histopathologic subtype and the typical anatomic sites of tumor involvement seen in children. Lymphoblastic lymphomas are most commonly supradiaphragmatic, presenting with a mediastinal mass and/or upper torso adenopathy. Children with abdominal tumors virtually always have undifferentiated lymphomas, either Burkitt or non-Burkitt. The primary sites of diffuse, so-called "histiocytic" or large cell lymphomas are variable, including nodal and extranodal sites, but skipping the anterior mediastinum.

One virtually never sees lymphocytic lymphomas of intermediate or well-differentiated types in children or diffuse mixed lymphocytic–"histiocytic" varieties of tumors. Likewise, although approximately half of all of the lymphomas seen in adults are nodular (follicular), this pattern is extremely rare in children. Frizzera and Murphy were able to compile only eight bona fide cases of nodular lymphomas in children aged less than 15 from a total of 318 cases of childhood lymphoma seen over a span of two decades at four cancer centers.[14] All of the cases seen in children were of the mixed or histiocytic nodular type, with nodular tumors of poorly differentiated lymphocytic type being notably absent. Confirming the scarcity, Winberg, Nathwani, and Rappaport found only 11 cases of nodular lymphomas in children and adolescents, aged less than 20, from a total of 1760 cases of nodular lymphomas.[15]

Using other classification schemes for lymphoma, such as the Kiel, all of the lymphomas encountered in childhood are high-grade, practically none are considered low-grade.[16] Autoradiographic studies of the labeling of tumor cells following in vitro exposure to tritiated thymidine have provided a kinetic explanation for this high-grade malignant growth pattern of childhood NHL.[17] The percentage of cells labelled was found to be correlated with the surface marker findings in lymphoproliferative disease in children, blasts with B cell markers (immunoglobulin-positive) having a significantly higher labeling than T cell blasts (sheep erythrocyte rosette-forming), both being higher than non-T, non-B leukemic blast cells. The surface-immunoglobulin positive tumor cells obtained from children with nonendemic Burkitt-like, or immunoblastic, tumors typically have labeling indices in vitro in the range of 30%–50%, the highest of any human tumor ever studied.[17] In contrast, where kinetic studies of low-grade, small cell, good prognosis lymphomas have been carried out in adults, a very low percentage of cells, generally 0.5%–2.0%, were in the DNA-synthetic phase of the cell cycle.[18] Conceivably, the growth rate of lymphoid malignancies, both in children and adults, is largely intrinsically regulated, reflecting the usual growth rate of the counterpart normal lymphoid cell subpopulation. The growth rate of B-cell lymphomas in children mirrors that of the immunoblast or noncleaved germinal center cell stimulated by antigen to proliferate.[17]

Characterization of the T- or B-cell nature of childhood NHL confirms a tumor cell differentiation state different from the majority of the lymphomas occurring in adult years, the tumors of children in general being more closely related to lymphoid stem cells and less functionally differentiated. Lymphoblastic lymphomas are T-cell derived, ordinarily contain terminal transferase, are reactive with antithymocyte sera, form variable percentages of nonimmune rosettes with sheep erythrocytes that are stable at 37°C, and may also have complement receptors[19,20]—all characteristics shared by fetal thymocytes. Undifferentiated lymphomas in childhood typically show intense surface fluorescence when reacted with anti-immunoglobulin reagents, the vast majority being B-cell derived regardless of whether morphologically Burkitt's or pleomorphic non-Burkitt's. In adults, the majority of B-cell lymphomas exhibit weaker surface fluorescence, being of cleaved follicular center cell origin.[20,21] The detection of B-cell markers on lymphoma cells may thus be of somewhat paradoxical prognostic significance, either good or bad, depending on the age of the patient and pattern of tumor immunopathology. In adults, lymphomas expressing B-cell markers exhibit a superior response to therapy, compared to T- or "null" cell tumors, the latter category having the worst prognosis.[22,23] In children, exactly the inverse relationship is true.[24,25] The best prognosis of all childhood lymphoproliferative disorders is associated with "null" cell leukemia (common ALL antigen positive, sheep erythrocyte-rosette negative, surface-immunoglobulin negative), and the worst with B-cell lymphomas, with T-cell disease, either leukemic or lymphomatous, of intermediate risk.

It is interesting to speculate on possible reasons for the different spectrum of B-cell disease seen in children compared to adults. In addition to the extreme paucity of nodular lymphomas already mentioned, children are not prone to well-differentiated lymphocytic lymphomas, chronic lymphocytic leukemia, or to plasma cell disorders, heavy chain disease, or myeloma. There may thus only be a narrow "window in ontogeny" defining susceptibility to oncogenic transformation.

DISEASE PRESENTATION AND STAGING

The distribution of the primary tumor sites observed in a total of 262 children from several series of childhood lymphomas, excluding children with evidence of leukemia at diagnosis, is shown in Table 2.[9,10,26–28] The predominant site of clinically detectable disease at presentation in the majority of children is extranodal, in contrast to the distribution of disease usually seen in adults. Only a minority of children, 37 of 262 (14%), exhibit primarily nodal involvement at diagnosis.

The most common location of disease in unselected series is intraabdominal, (Table 2, 91 of 262, 35%) either involving the gastrointestinal tract primarily or presenting with extensive intra-abdominal tumor manifested by ascites and massive tumor formation in the small bowel, mesentery, retroperitoneum, and omentum. The

Table 2. Distribution of Primary Anatomic Sites of Tumor Involvement Seen in Childhood NHL at the Time of Diagnosis*

Primary Site	Frequency of Involvement					
	Murphy[10]	Murphy[9]	Jenkin[26]	Jaffe[27]	Hausner[28]	Totals
Abdomen	25 (36%)†	10 (32%)	39 (40%)	7 (23%)	10 (33%)	91 (35%)
Mediastinum	18 (26%)	5 (16%)	24 (24%)	10 (33%)	11 (36%)	68 (26%)
Head–neck‡	12 (17%)	4 (13%)	11 (11%)	4 (13%)	4 (13%)	35 (13%)
Peripheral nodes	7 (10%)	5 (16%)	21 (21%)	2 (6%)	2 (6%)	37 (14%)
Other§	7 (10%)	7 (22%)	7 (6%)	7 (23%)	3 (10%)	31 (11.8%)
Totals	69 (100%)	31 (100%)	102 (100%)	30 (100%)	30 (100%)	262 (100%)

*Excluding children with evidence of leukemia at diagnosis.

†Number of children (%).

‡Includes Waldeyer's ring, sinus(es), and/or unilateral or bilateral cervical or supraclavicular lymph nodes.

§Includes bone, epidural space, breast, gonad, orbit, skin, and mixed multicentric foci of disease.

usual site for tumor formation in the gastrointestinal tract in children is the distal ileum, appendix, and cecum. Unlike the pattern of gastrointestinal involvement observed in adults,[27] involvement of the stomach or colon is notably absent in children. Jones et al. observed that the identification of initial gastrointestinal involvement by a diffuse lymphoma in adulthood implied an extremely grave prognosis.[29] The same may be said for children with the exception of the minority of fortunate children with intra-abdominal tumors whose disease is limited to a segment of the gut, plus or minus the associated mesenteric nodes only, and the primary tumor can be completely removed grossly by segmental excision. Such children (Table 3, Stage II or AR) are highly curable, enjoying a 90%–100% expectation of disease-free survival with modern therapy.[10,26,30]

Mediastinal lymphomas are the next most common site of primary tumor involvement in children (Table 2, 68 of 262, 26%). Clinically the disease presentation is almost stereotyped, with a 2–4 wk history of malaise and cough progressing to dyspnea due to the presence of an anterior mediastinal mass, often in association with a pleural effusion, and sizeable cervical and supraclavicular adenopathy. Children, even with apparently localized mediastinal tumors established by lymphangiography and/or laparotomy, are not effectively treated with involved or extended field radiation.[31] The natural propensity of mediastinal lymphomas in children is to disseminate rapidly in a noncontiguous fashion to involve the bone marrow, central nervous system, and gonads. In a retrospective review of cases seen at the Farber Center and Children's Hospital Medical Center from 1947–1972, Jaffe et al. observed a leukemic transformation in 49 of 58 cases of mediastinal lymphomas in children (84.5%).[27] The prognosis for children with mediastinal lymphomas is still grave, though recent encouraging reports of 80% or greater 2-yr survival, when treated either with the multi-drug LSA_2-L_2 or "APO" regimens,[32,33] may indicate a significant treatment-induced alteration in the natural history of the disease process. The current indication then for combination chemotherapy for mediastinal lymphomas obviates somewhat the need for scrupulous surgical-pathologic staging.

The exact frequency of bone marrow involvement at diagnosis of children with NHL is impossible to designate due to case selection in reported series and non-uniform discrimination between lymphoma and leukemia in children. At St. Jude Children's Research Hospital, we have arbitrarily but conventionally defined lymphoma as stage IV on the basis of marrow involvement whenever initial marrow aspirates were unequivocally positive for lymphoma cells but less than 25% of the marrow cell differential was involved. Using that criteria, 11 of the last 69 consecutive cases seen (15.9%) had initial marrow involvement.[10] Rather remarkably, Jones et al. likewise reported 15% marrow involvement on presentation in adults with diffuse lymphomas.[29] Unlike the general experience in staging procedures in adults, however, we have not found the bone marrow biopsy to be particularly useful for detection of marrow involvement in children.[34] We have never encountered the clinical instance in a child when the bone marrow biopsy has revealed marrow involvement by lymphoma not already apparent from inspection of a smeared marrow aspirate.[32] The marrow aspirate is more

Table 3. Alternate Clinical Staging Systems for Childhood Lymphomas

Author	Stage	Criteria for Extent of Disease
Murphy[10,37]	I	A single tumor (extranodal) or single anatomic area (nodal), with the exclusion of mediastinum or abdomen.
	II	A single tumor (extranodal) with regional node involvement. Two or more nodal areas on the same side of the diaphragm. Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm. A primary gastrointestinal tract tumor, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only.
	III	Two single tumors (extranodal) on opposite sides of the diaphragm. Two or more nodal areas above and below the diaphragm. All the primary intra-thoracic tumors (mediastinal, pleural, thymic). All extensive primary intra-abdominal disease. All paraspinal or epidural tumors, regardless of other tumor site(s).
	IV	Any of the above with initial CNS and/or bone marrow involvement.
Wollner[32]	I	One single site
	II	Two or more sites on the same side of the diaphragm.
	III	Disseminated disease without marrow or central nervous system involvement.
	IV	Any of the above with bone marrow and/or central nervous system involvement.
Ziegler[39]*	A	Single solitary extra-abdominal site.
	AR	Intra-abdominal tumor with >90% of tumor surgically resected.
	B	Multiple extra-abdominal sites.
	C	Intra-abdominal tumor.
	D	Intra-abdominal tumor with involvement of ≥1 extra-abdominal site.

*Applicable to Burkitt-like lymphomas only.

The alternate staging systems in use for childhood lymphomas share some features in common. All make no distinction between primary nodal and extra nodal presentations for staging purposes. Each recognizes the existence of either bone marrow or central nervous system involvement or both as being indicative of a grave prognosis, i.e., stage IV. Two of the schemes specifically recognize the better prognosis associated with grossly complete (>90%) resection of intra-abdominal disease (stage II in the St. Jude system being equivalent to Ziegler's AR).

sensitive than the biopsy for detection of small numbers of tumor cells in an otherwise normal marrow. The low yield and insensitivity of the marrow biopsy for detection of bone marrow involvement in children is probably due to the deficiency of nodular forms or lymphocytic histologic subtypes.

The minimum requisite staging procedures for children newly diagnosed with lymphoma consist of a careful physical examination, complete blood count, chest roentgenogram, bone marrow aspirate, lumbar puncture and examination of a cytocentrifuged specimen of spinal fluid, and renal and hepatic function tests. Additional examinations, such as liver–spleen scans, bone scans, or ultrasound or computerized axial tomography of the abdomen and pelvis, provide useful baselines to monitor the response to therapy but seldom reveal foci of disease not otherwise suspected clinically. A pretreatment staging laparotomy is not indicated for children with NHL in light of the current therapeutic philosophy. Since no child should receive only radiotherapy for treatment, a scrupulous search for microscopic disease that may be outside of any proposed radiation portals is unnecessary, produces undue delay in treatment, and only risks added morbidity. However, a laparotomy is usually necessary for diagnosis or relief of obstruction or intussusception in children who present with abdominal disease. At the time of such surgery, an effort to achieve a grossly complete tumor resection should be made, if at all possible, in view of the improvement in survival reported to result from surgical bulk reduction of tumor.[35]

Based on the results of staging procedures, it is conventional practice to assign a stage denoting the extent of disease. Staging designations facilitate clear communication and interpretation of end results and have traditionally also been helpful in guiding the assessment of prognosis and in assisting therapeutic decision-making. To that end, it has been the standard practice to use the Ann Arbor staging classification, developed for use in Hodgkin's disease, for NHL as well. Unfortunately, the Ann Arbor system is of only limited value for lymphomas other than Hodgkin's disease, suffering from major deficiencies, both when applied to adults,[36] and to children. The Ann Arbor system is ill-suited for continued use in children firstly

for anatomic reasons: the predominant extra nodal involvement, the noncontiguous nature of disease spread, and the tendency for leukemic evolution and involvement of the central nervous system. The rarity of true stage III disease in children is likewise notable, 3 of a total of 233 childhood cases (1.2%) from 3 published series using the Ann Arbor scheme.[9,27,38] Secondly, the Ann Arbor staging system fails to assist in therapeutic decision making since current procedures fail to identify any child who can be treated definitively with radiotherapy alone. Consequently the emphasis on invasive surgical pathologic staging placed in the Ann Arbor classification is ill-placed in staging children.

As a result of the deficiencies of the Ann Arbor scheme, alternative approaches to staging childhood lymphomas have been proposed. These are outlined for comparison in Table 3.[10,32,37,39] Ziegler's schema is applicable to undifferentiated or Burkitt lymphomas, while the other two schemes are applicable to lymphomas of any histology. All schemes share simplicity and make no distinction between primary nodal and extra nodal presentations for staging purposes. While all of the schemes provide useful prognostic information, none of these alternatives is exactly ideal. Despite recognizing the major site(s) of tumor involvement for assignment of stage, the staging designations themselves fail to convey prognostically important information about primary tumor site or possible reasons for classifying a patient as stage IV. For example, stage I axillary nodal disease may differ significantly from stage I orbital or tonsillar disease in its relapse hazard, particularly in the meninges. The staging classifications might be improved by subscripts identifying stage IV patients as either M+ or M− and/or CNS+ or CNS−, in a fashion similar to that recommended by the Ann Arbor classification, since the prognosis of stage IV disease with central nervous system involvement is far more grave than with bone marrow involvement only.[32]

Lacking a generally accepted staging system for childhood NHL, it is the current practice of some centers and pediatric cooperative groups, like the Children's Cancer Study Group (CCSG), to use no formal staging system, adopting a uniform treatment policy and distinguishing only those children with grossly localized forms of lymphoma from all others for prognostic purposes only.[38] Children's Cancer Study Group classifies children with lymphoma as having localized or regional disease provided they have disease limited to either one or two adjacent lymphatic regions, Waldeyer's ring with or without regional nodes, the gastrointestinal tract with or without involvement of regional nodes limited to the mesentery, or any other localized extra lymphatic site with or without regional nodes. In practice, the definition of such patients with grossly localized lymphomas by CCSG corresponds to the SJCRH classification of stage I and II disease. Roughly 30% of all cases of childhood NHL fall into stages I and II. The importance of recognizing such presentations in childhood lymphomas stems from their extremely good prognosis. Several reports confirm a 100% frequency of attainment of a complete response with intensive combined modality therapy and an overall 90%–95% cure rate can be expected for these patients.[10,32,40–44]

Obviously some refinements in staging and classification of children with NHL are needed, since present staging systems actually only distinguish two groups of patients, i.e., those with a good prognosis (stages I and II, or A, B, and AR) from all others (stage III and IV, or C and D). The latter group is mixed, being composed of children with tumors in varying primary locations (intrathoracic versus intra-abdominal or multicentric) with differing tumor cell characteristics. Treatment regimens useful for stage III or IV lymphoblastic tumors (T-cell derived) have been notably less useful when applied to advanced-stage undifferentiated or Burkitt-like tumors (B-cell derived).[44,45] Rational selection of therapeutic approaches and design of clinical trials in the next decade would be aided by a comprehensive pretreatment assessment of the tumor cell characteristics, primary site, and extent of disease. Greater sophistication in patient subgrouping may yield new insights into the biology of the childhood lymphomas, potentially unmasking important differences in responses to therapeutic intervention.

END RESULTS AND LATE EFFECTS OF TREATMENT

Treatment of the child with lymphoma differs fundamentally from the adult, the essence of the

difference being the sensitivity of target tissues, both neoplastic and normal. The childhood lymphomas are typically exquisitely sensitive to initial therapy, and the frequency of complete responses ordinarily approximates 85%–95% of all patients.[10,32,43] A large proportion of all children are curable, including 90%–100% of the children with localized disease and a lesser but still significant fraction with generalized disease. The overall 2-yr survival of several recently reported series, including children of all stages and histologies, is 61%–76%.[10,32,41-43] In contrast to the continuous relapse hazard observed in adults with lymphocytic lymphoma,[46] the relapse hazard in children is greatest in the first 6–12 mo from diagnosis, and relapses after 2 yr are not commonly observed.[25,38] Consequently, more than half of all children with lymphomas are curable with modern therapy. Considering the extended number of years at risk for late effects, there is therefore an appropriately greater concern over the sensitivity of the child to the adverse long-term consequences of treatment, especially radiation.[47-49] Li et al. have estimated the 20-yr cumulative probability of a second cancer as 12% in a series of survivors of childhood cancer.[48] Available published data assessing the risk of a second neoplasm in children who survive the first cancer dates back to a treatment era when orthovoltage radiation equipment and either no or modest single-agent chemotherapy were the norm. Assuming the median oncogenic latent period is 15–20 yr, the rate of second neoplasms may be seriously underestimated. Several of the chemotherapeutic agents in use in current intensive lymphoma regimens are known to be radiation enhancers, carcinogens, and mutagens. If chemotherapy in any way influences the rate of induction of a second neoplasm in children cured of lymphoma, then it is far too early to precisely estimate the oncogenic potential of current treatment protocols that have only really exerted their major impact on survival in the last decade of the seventies.

Regimens in current use for the treatment of childhood lymphomas most commonly rely on multiple drugs in combination, vincristine, prednisone, high-dose cyclophosphamide, adriamycin, moderate-to-high-dose methotrexate, as well as other agents, usually combined with radiotherapy to the site(s) of bulk disease. The usual overall duration of therapy is 2.5–3 yr, significantly longer than most chemotherapy protocols used for the treatment of adult lymphomas. The management of childhood lymphomas has recently been reviewed,[50,51] but can hardly be considered standardized. The contribution of radiotherapy to an effective multidrug protocol, the most effective and least toxic form of CNS prophylaxis for certain subgroups of children, the optimum regimen and duration of maintenance therapy after induction of a complete remission, and the possibility of a reduction in the intensity of therapy for children with a good prognosis are specific questions that must be examined in future controlled clinical trials.

REFERENCES

1. Smith NJ, Vaughan VC: The lymphatic system, in Nelson WE (ed): Textbook of Pediatrics, (ed 8). Philadelphia, Saunders, 1964, p 1074
2. Holt LE: The diseases of infancy and childhood. New York, D. Appleton, 1899, pp 816–818
3. Zuelzer WW, Kaplan J: The child with lymphadenopathy. Semin Hematol 12:323–334, 1975
4. Young JL, Miller RW: Incidence of malignant tumors in U.S. children. J Pediatr 86:254–258, 1975
5. Williams AO: Tumors of childhood in Ibadan, Nigeria. Cancer 36:370–378, 1975
6. Aghai E, Hulu N, Virag I, Kende E, et al: Childhood non-Hodgkin's lymphoma—A study of 17 cases in Israel. Cancer 33:1411–1416, 1974
7. Elias L: Differences in age and sex distributions among patients with non-Hodgkin's lymphoma. Cancer 43:2540–2546, 1979
8. Purtilo DT: Opportunistic non-Hodgkin's lymphoma in X-linked recessive immunodeficiency and lymphoproliferative syndromes. Semin Oncol 4:335–343, 1977
9. Murphy, SB, Frizzera G, Evans AE: A study of childhood non-Hodgkin's lymphoma. Cancer 36:2121–2131, 1975
10. Murphy SB, Hustu HO: A randomized trial of combined modality therapy of childhood non-Hodgkin's lymphoma. Cancer 45:630–637, 1980
11. Cossman J, Berard CW: Histopathology of childhood non-Hodgkin's lymphomas, in Graham-Pole J (ed): Progress in Pediatric Hematology/Oncology. Littleton, Massachusetts, PSG Publishing (in press)
12. Dorfman R: Pathology of the non-Hodgkin's lymphomas: New classifications. Cancer Treat Rep 61:945–951, 1977 (and personal communication)
13. Nathwani BN, Kim H, Rappaport H: Malignant lymphoma, lymphoblastic. Cancer 38:964–983, 1976
14. Frizzera G, Murphy SB: Follicular (nodular) lymphoma in childhood: A rare clinical pathologic entity. Report of eight cases from four cancer centers. Cancer 44:2218–2235, 1979
15. Winberg C, Nathwani BH, Rappaport H: Nodular

(follicular) lymphomas in children and young adults: A clinicopathologic study of 64 patients. Lab Invest 40:282, 1979 (abstr)

16. Lennert K: Klassifikation der non-Hodgkin lymphome in kindesalter. Klin Pädiat 189:7–13, 1977

17. Murphy SB, Melvin SL, Mauer AM: Correlation of tumor cell kinetic studies with surface marker results in childhood non-Hodgkin's lymphomas. Cancer Res 39:1534–1538, 1979

18. Silvestrini R, Piazza R, Riccardi A, et al: Correlation of cell kinetic findings with morphology of non-Hodgkin's malignant lymphomas. J Natl Cancer Inst 58:499–504, 1977

19. Coccia PF: Characterization of the blast cell in childhood non-Hodgkin's lymphoproliferative malignancies. Semin Oncol 4:287–296, 1977

20. Mann RB, Jaffe ES, Berard CW: Malignant lymphomas—A conceptual understanding of morphologic diversity. Am J Pathol 94:105–192, 1979

21. Leech JH, Glick AD, Waldron JA, et al: Malignant lymphomas of follicular center cell origin in man. I. Immunologic studies. J. Natl Cancer Inst 54:11–21, 1975

22. Bloomfield CD, Kersey JH, Brunning RD, et al: Prognostic significance of surface markers in adult non-Hodgkin's malignant lymphoma. Lancet 2:1330–1333, 1976

23. Bloomfield CD, Gajl-Peczalska J, Frizzera G, et al: Clinical utility of lymphocyte surface markers combined with the Lukes–Collins histologic classification in adult lymphoma. N Engl J Med 301:512–518, 1979

24. Coccia PF, Kersey JH, Gajl-Peczalska K, et al: Prognostic significance of surface marker analysis in childhood non-Hodgkin's lymphoproliferative malignancies. Am J Hematol 1:405–417, 1976

25. St. Jude's Children's Research Hospital: Unpublished results

26. Jenkin RDT: The management of malignant lymphoma in childhood, in Deeley TJ (ed): Modern Radiotherapy—Malignant Diseases in Children. London, Butterworths, 1973, pp 341–359

27. Jaffe N, Buell D, Cassady JR, et al: Role of staging in childhood non-Hodgkin's lymphoma. Cancer Treat Rep 61:1001–1007, 1977

28. Hausner RJ, Rosas-Uribe A, Wickstrum DA, et al: Non-Hodgkin's lymphoma in the first two decades of life. Cancer 40:1533–1547, 1977

29. Jones SE, Fuks Z, Bull M, et al: Non-Hodgkin's lymphomas. IV. Clinicopathologic correlation in 405 cases. Cancer 31:806–823, 1973

30. Nelson DR, Cassady JR, Traggis D, et al: The role of radiation therapy in localized resectable intestinal non-Hodgkin's lymphoma in children. Cancer 35:89–97, 1977

31. Glatstein E, Kim H, Donaldson SS, et al: Non-Hodgkin's lymphomas. VI. Results of treatment in childhood. Cancer 34:204–211, 1974

32. Wollner N, Burchenal JH, Lieberman PH, et al: Non-Hodgkin's lymphoma in children. A comparative study of two modalities of therapy. Cancer 37:123–134, 1976

33. Weinstein H, Vance Z, Jaffe N, et al: Improved prognosis for patients with mediastinal lymphoblastic lymphoma. Blood 53:687–694, 1979

34. Murphy SB, Caces J: Limited utility of bone marrow biopsy in staging children with non-Hodgkin's lymphoma (NHL). Blood 52(suppl 1):265, 1978

35. Magrath IT, Lwanga S, Carswell W, et al: Surgical reduction of tumour bulk in management of abdominal Burkitt's lymphoma. Br Med J 2:308–312, 1974

36. Rosenberg SA: Validity of the Ann Arbor staging classification for the non-Hodgkin's lymphomas. Cancer Treat Rep 61:1023–1027, 1977

37. Murphy SB: Prognostic features and obstacles to cure of childhood non-Hodgkin's lymphoma. Semin Oncol 4:265–271, 1977

38. Lemerle M, Gerard-Marchant R, Sarrazin D, et al: Lymphosarcoma and reticulum cell sarcoma in children. Retrospective study of 172 cases. Cancer 32:1499–1507, 1973

39. Ziegler J, Magrath I: Burkitt's lymphoma. Pathobiol Annu 4:129–142, 1974

40. Jenkin R, Anderson J, Chilcote R, et al: Grossly localized childhood non-Hodgkin's lymphoma (NHL). Response to irradiation and elective 4 or 10 drug combination chemotherapy. Proc ASCO 20:354, 1979

41. Gout-Lemerle M, Rodary C, Sarrazin D: Treatment of children with non-Hodgkin malignant lymphoma. Arch Fr Pediatr 33:537–553, 1976

42. Brecher M, Freeman AI, Sinks LF, et al: Non-Hodgkin's lymphoma in children. Cancer 41:1997–2001, 1978

43. Carabell SC, Cassady JR, Weinstein HJ, et al: The role of radiation therapy in the treatment of non-Hodgkin's lymphomas. Cancer 42:2193–2205, 1978

44. Weinstein H, Buell D, Cassady JR, et al: Improved prognosis for childhood non-Hodgkin's lymphomas. Blood 50:(suppl 1)212, 1977

45. Ramirez I, Sullivan MP, Wang Y, et al: Effective therapy for Burkitt's lymphoma: High-dose cyclophosphamide + high-dose methotrexate with coordinated intrathecal therapy. Cancer Chemother Pharmacol 3:103–109, 1979

46. McKelvey EM, Moon TE: Curability of non-Hodgkin's lymphomas. Cancer Treat Rep 61:1185–1190, 1970

47. Li FP, Cassady JR, Jaffe N: Risk of second tumors in survivors of childhood. Cancer 35:1230–1235, 1975

48. Meadows AT, Krejmas NL, Belasco JB: The medical cost of cure, in Van Eys Jr, Sullivan MP (eds): Status of the Curability of Childhood Cancers. New York, Raven, 1980, pp 263–275

49. Littman PS, D'Angio GJ: Growth considerations in the radiation therapy of children with cancer. Annu Rev Med 30:405–415, 1979

50. Murphy SB; Management of childhood non-Hodgkin's lymphoma. Cancer Treat Rep 61:1161–1173, 1977

51. Weinstein HJ, Link MP: Non-Hodgkin's lymphoma in childhood. Clinics in Haematology 8, No 3, Oct 1979 pp 699–713