Non-Hodgkin Lymphoma

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9.1 Introduction

Non-Hodgkin lymphoma is a heterogeneous group of lymphoid malignancies. The overall incidence and frequency of the different histological subgroups varies according to age at diagnosis. Adolescence is at the junction of childhood and adulthood in the sense that, in adolescents, the lymphomas frequent in children and rare in adults may still be seen (the Burkitt and the lymphoblastic types), but the incidence of the large cell subtypes, especially the diffuse large B-cell lymphomas, frequent in adults, increases greatly in young adults (to 30 years of age).

In many countries, the minority of adolescents are referred to pediatric departments where they are generally included in trials, but the majority are referred to adult departments where a minority are registered in trials. So far, there are few data on adolescents and young adults with non-Hodgkin lymphoma. The questions are: is there a difference in results when patients are treated with childhood versus adult non-Hodgkin lymphoma protocols and in their respective departments? If yes, is it related to the type of treatment? Is there a prognostic value of age of onset and treatment with similar therapeutic strategies? Is this related to different biology? In this chapter we will present what is presently known, but many questions are still without answers, which indicates the need for further studies directed specifically toward adolescents and young adults with non-Hodgkin lymphoma.
9.2 Epidemiology

9.2.1 Age-Specific Incidence

The overall incidence of non-Hodgkin lymphoma increases steadily with age (Table 9.1 and Fig. 9.1), in contrast to Hodgkin lymphoma, which peaks in early adulthood, declines in incidence with age, and increases again in late adulthood (Fig. 9.1) [1]. During the past quarter century in the United States, the incidence of non-Hodgkin lymphoma has increased in each age group through to age 30 years (Table 9.1). In 20- to 29-year-olds, the increase was dramatic, averaging 4–19% per year over 25 years. Most of the increase was in the non-Burkitt, non-Hodgkin Lymphoma category II(b), according to the International Classification of Childhood Cancer (ICCC), which was in part due to the human immunodeficiency virus (HIV) epidemic that occurred during the 1980s and early 1990s (Table 9.1). In the 1979–1997 English registry, non-Hodgkin lymphoma represented 7% of all cancers in adolescents, very similar to the corresponding proportion in the United States.


<table>
<thead>
<tr>
<th>Age at diagnosis (years)</th>
<th>&lt;5</th>
<th>5–9</th>
<th>10–14</th>
<th>15–19</th>
<th>20–24</th>
<th>25–29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hodgkin lymphoma, <em>ICCC</em> II(b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average incidence per million, 1975–2000, SEER</td>
<td>3.4</td>
<td>5.4</td>
<td>7.1</td>
<td>11.7</td>
<td>16.5</td>
<td>27.3</td>
</tr>
<tr>
<td>Average annual % change in incidence, 1975–2000, SEER</td>
<td>na</td>
<td>0.2%</td>
<td>2.2%</td>
<td>2.3%</td>
<td>3.6%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Estimated incidence per million, year 2000, United States</td>
<td>2.8</td>
<td>5.5</td>
<td>8.8</td>
<td>14.3</td>
<td>21.8</td>
<td>39.3</td>
</tr>
<tr>
<td>Estimated number of persons diagnosed, year 2000, U.S.</td>
<td>66</td>
<td>110</td>
<td>147</td>
<td>290</td>
<td>413</td>
<td>762</td>
</tr>
<tr>
<td>Burkitt and other non-Hodgkin lymphoma, <em>ICCC</em> II(c), II(d), and II(e)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average incidence per million, 1975–2000, SEER</td>
<td>2.8</td>
<td>3.7</td>
<td>3.9</td>
<td>3.1</td>
<td>3.6</td>
<td>7.5</td>
</tr>
<tr>
<td>Average annual % change in incidence, 1975–2000, SEER</td>
<td>na</td>
<td>–1.0%</td>
<td>–0.7%</td>
<td>1.6%</td>
<td>9.8%</td>
<td>18.5%</td>
</tr>
<tr>
<td>Estimated incidence per million, year 2000, United States</td>
<td>1.9</td>
<td>3.2</td>
<td>3.6</td>
<td>3.5</td>
<td>5.6</td>
<td>12.5</td>
</tr>
<tr>
<td>Estimated number of persons diagnosed, year 2000, U.S.</td>
<td>54</td>
<td>76</td>
<td>81</td>
<td>72</td>
<td>108</td>
<td>243</td>
</tr>
</tbody>
</table>
Chapter 9

9.2.2 Incidence of Histologic Types

When analyzed according to histologic type of non-Hodgkin lymphoma, the greatest change in the distribution of the subtypes over the 15- to 29-year age span is the appearance of follicular (nodular) lymphoma which, during the period 1992–2002, was virtually nonexistent before age 15 years and increased in relative proportion to 11% among 25- to 29-year-olds (Fig. 9.2). Diffuse small-cell lymphoma also increased, and mantle cell lymphoma made its appearance in 15- to 29-year olds. The incidence of lymphoblastic lymphoma (LL) and Burkitt lymphoma decreased as a function of age from the 15- to 19-year age interval to the 25- to 29-year interval.

The French-American-British (FAB) LMB96 study, a 5-year prospective international study for the treatment of B-cell lymphoma in children and adolescents, was not a population-based registry, but interestingly some differences were observed between the three countries in terms of repartition of the two subgroups of B-cell non-Hodgkin lymphoma. After adjusting for age, diffuse large B-cell lymphoma (DLBCL) was more frequent in the United States than in the European countries, especially in France [2, 3].

9.2.3 Gender-Specific Incidence

Non-Hodgkin lymphoma was more common among males than females for all ages up to 45 years. In non-Burkitt, non-Hodgkin lymphoma (ICCC category IIb), the male:female ratio increased over this age interval to nearly twofold greater in males (Fig. 9.3).

In Burkitt lymphoma, the male predominance is striking, with male:female ratios approaching 6 for the 5- to 14-year and 25- to 44-year age groups (Fig. 9.4). Females in the 15- to 24-year age group had a higher incidence of Burkitt lymphoma relative to males than in younger or older age groups, with a male:female ratio at a nadir of 2.6–3.2 (Fig. 9.4).

9.2.4 Racial/Ethnic Differences in Incidence

Figure 9.5 displays the incidence of all non-Hodgkin lymphoma as a function of race/ethnicity. Incidence increased for all groups as a function of age. A switchover from the highest rate among non-Hispanic whites and Asians/Pacific Islanders to the highest rate among African Americans/blacks occurred at about 20 years of age. At all ages, American Indians/Alaska Natives had the lowest incidence of non-Hodgkin lymphoma.
Whatever the age, it is known that a few patients are at increased risk of developing non-Hodgkin lymphoma: those with congenital or acquired immunodeficiency and those receiving immunosuppressive therapy (such as after organ transplantation). The incidence is significantly higher in males than in females, and is higher in whites than African Americans/blacks, as reviewed earlier. Specific geographical areas are also recognized for particular types of lymphoma, such as the “endemic” (African) Burkitt lymphoma. Other risk factors include Epstein-Barr virus (EBV) or *Helicobacter pylori* infection, tobacco, and chemical or other environmental exposure. In underdeveloped countries, there is a documented link between EBV and Burkitt lymphoma, while in the developed world EBV is also associated with other subtypes of non-Hodgkin lymphoma. Secondary neoplasms are well-documented sequelae of HIV infection, and account for an increase in non-Hodgkin lymphoma incidence, particularly in males. The increase in non-Hodgkin lymphoma has persisted in the face of a stabilization of the incidence of new cases of HIV and with improved treatments for the infection. A few familial cases of lymphoid malignancies have been observed, without apparent recognized genetic abnormalities.

Classification of non-Hodgkin lymphoma has changed many times over the years and became more distinct with the increased understanding of lymphomagenesis and the development of new diagnostic tools (immunophenotyping, cytogenetics, molecular biology, and now gene profiling). The current World Health Organization (WHO) classification [4], preceded by the Revised American European Lymphoma (REAL) classification [5], is now widely used. Microarray technologies, by studying the expression of many genes at once, are very promising [6], but their implication for diagnosis and prognosis, and their further utility in clinical practice, especially in adolescence and young adults, require further investigation. The characteristics of the four categories of lymphoma most frequently encountered in adolescents and young adults (Burkitt, LL, DLBCL and anaplastic large cell, ALCL) are demonstrated in Table 9.2.
<table>
<thead>
<tr>
<th></th>
<th>Burkitt</th>
<th>Lymphoblastic</th>
<th>Large B-cell</th>
<th>Anaplastic large cell</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferential tumor site</strong></td>
<td>abdomen, head and neck</td>
<td>mediastinum (T cell)</td>
<td>abdomen, thymus, bone</td>
<td>node, skin</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cell size</td>
<td>medium, narrow, basophilic, with vacuoles round, several nuclei</td>
<td>medium narrow, pale</td>
<td>large</td>
<td>voluminous</td>
</tr>
<tr>
<td>cytoplasm</td>
<td></td>
<td></td>
<td></td>
<td>abundant and clear erythrophagocytosis</td>
</tr>
<tr>
<td>nucleus</td>
<td></td>
<td></td>
<td></td>
<td>irregular, clear</td>
</tr>
<tr>
<td>nucleoli</td>
<td></td>
<td></td>
<td></td>
<td>voluminous</td>
</tr>
<tr>
<td>chromatin</td>
<td>coarse and irregular</td>
<td>finely stippled</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FAB equivalent</strong></td>
<td>L3</td>
<td>L1, L2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Immunophenotyping</strong></td>
<td>CD20+, CD79a+, Slg+, Ki 67+&gt;95%</td>
<td>TdT+, B lineage T lineage</td>
<td>CD20+, CD79a+, Slg +/−</td>
<td>CD30+, EMA+, ALK+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CD19+, CD7+</td>
<td>bcl6 +/-</td>
<td>(T or “null” markers)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CD 79a+, CD2+</td>
<td>Ki 67 : 60 – 90%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slg−, CD3c+ cMu −/+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cytogenetics</strong></td>
<td></td>
<td>no specific abnormalities, sometimes involvement of T-cell antigen receptor genes (TCR) on chromosome 7(q34) or 14(q11)</td>
<td>Sometimes t(8;14)(q24;q32) or variant der (3)(q27) (bcl6)</td>
<td>t(2 ;5) (p23 ;q35) or variant</td>
</tr>
<tr>
<td><strong>Result</strong></td>
<td>transcriptional deregulation of c-MYC</td>
<td>transcriptional deregulation of bcl6</td>
<td>NPM/ALK fusion protein; ALK is a tyrosine kinase receptor located on 2p23</td>
<td></td>
</tr>
</tbody>
</table>
9.5 Clinical Features

The clinical presentation of non-Hodgkin lymphoma in adolescents and young adults, as in other age classes, varies and depends on the primary site of the disease, the histological subtype, and the extent of the disease. Burkitt lymphoma generally arises in the abdomen (digestive track) and in the Waldeyer ring, while LL generally arises from the thymus. Burkitt abdominal lymphoma generally presents as a large and rapidly growing abdominal mass that is often associated with ascites and other intra- or extraabdominal involvement. Intussusception leading to the discovery of a small excisable abdominal tumor is a rare presentation that is related to Burkitt or DLBCL. Extensive abdominal surgery should be avoided. The diagnosis can be made on surgical biopsy, but also on cytological examination of a serous effusion or on percutaneous needle biopsy of the tumor.

Lymphoblastic mediastinal lymphoma leads to mediastinal compression, which may be life threatening (general anesthesia should be avoided if possible) and is often associated with a concomitant pleural effusion. Therefore, the diagnosis should be made using cytological examination of effusions or bone marrow smears. If a tumor biopsy is needed, then this should be done by percutaneous needle biopsy or by mediastinoscopy. Another lymphoma arising in the thymus is the primary mediastinal B-cell lymphoma of thymus origin, which may present with pericarditis, pulmonary nodules and/or subdiaphragmatic involvement such as the kidney and pancreas.

Head and neck primary sites including Waldeyer’s ring and the facial bones are more often seen in Burkitt lymphoma. In the less frequent sites such as superficial lymph nodes, bone, skin, thyroid, orbit, eyelid, kidney, and epidural space, any subtype of lymphoma can be seen, emphasizing the necessity of a good-quality sample for histology and immunophenotyping.

ALCLs present with more unique features: usually nodal involvement, sometimes painful, which is characteristic of this disease; frequent skin involvement with inflammatory symptoms of the involved nodes, distant macular lesions, or general skin modification resembling ichthyosis; frequent general symptoms with widely fluctuating fever; and “wax and wane” evolution in a few cases with previous episode(s) of spontaneous regression.

9.6 Initial Work-Up and Staging

Diagnosis can be obtained utilizing biopsy material including tumor-touch preparations, but also cytological examination of effusion fluids or bone marrow smears, so surgical procedures can be avoided in diffuse Burkitt and lymphoblastic diseases. Also strongly recommended are the immunological and cytogenetic or molecular biology studies.

Once the diagnosis of non-Hodgkin lymphoma has been made, a speedy assessment of diagnosis, staging, and general evaluation must be done in order to commence appropriate treatment as soon as possible. This is particularly important in Burkitt lymphoma and LL, which have a great propensity to spread rapidly both regionally and systemically, especially in the bone marrow and in central nervous system (CNS).

Staging classifications are different in children, where the St Jude (also called Murphy) classification [7] is used because of the predominance of extranodal primaries, and in adults where the Ann Arbor classification, more adapted to nodal disease, is used (Table 9.3). These two different staging systems between children and adults make comparisons between pediatric and adult studies difficult, particularly in the adolescent and young adult age range. Also utilized for therapeutic classification in adults is the International Prognostic Index (IPI) based on stage, serum lactate dehydrogenase (LDH) levels, and Performance Status (PS). PS does not seem appropriate for very fast-growing tumors such as Burkitt and lymphoblastic, and is often not documented in pediatric lymphoma trials. This might make comparisons difficult between childhood and adult studies, especially in large-cell lymphoma. PS should be included in future studies that include adolescents. In spite of being an unspecific marker and of different methods of dosage with different “norms”, serum LDH level is a very good indicator of tumor burden and generally has prognostic significance.

The traditional boundary between leukemia and lymphoma has been defined arbitrarily by more or less
than 25% blast cells in the bone marrow, but this does not correspond to either clinical or biological differences. CNS involvement is defined by the presence of unequivocal malignant cells in a cytocentrifuged specimen of spinal fluid and/or the presence of obvious neurological deficits, such as cranial nerve palsies.

Experience with positron emission tomography in childhood and adolescent non-Hodgkin lymphoma is in the early stages of investigation. It is hoped that this diagnostic tool will help to predict the presence of active tumors in a residual mass.

Patients often have other problems at diagnosis, such as malnutrition, infection, postsurgical complications, and respiratory and metabolic abnormalities; these may be life threatening or compromise the onset of therapy. Tumor lysis syndrome may be present at diagnosis or may develop during treatment. In advanced diseases, especially in Burkitt lymphoma and LL, preventive measures must always be instituted: hyperdiuresis and “uricolytic” drugs (allopurinol or urate oxidase). Urate oxidase should be utilized in cases of high tumor burden [8–11]. Urate oxidase con-
verts uric acid into allantoin, which is highly soluble in urine. It is an efficient way of promptly reducing serum uric acid levels, thus preventing uric acid nephropathy and preserving renal function, allowing a better excretion of the other cell metabolites such as potassium and phosphorus. Strict clinical and metabolic monitoring of patients during the lysis phase is essential.

### 9.7 B-Cell non-Hodgkin Lymphoma

The two main entities of B-cell non-Hodgkin lymphoma are Burkitt and DLBCL. The other B-cell non-Hodgkin lymphomas, such as the follicular, mantle cell, or the mucosa-associated lymphoid tissue lymphomas, are not often encountered in adolescents and young adults and will not be discussed in this chapter.

#### 9.7.1 Burkitt Lymphoma

Burkitt lymphoma is characterized by a high proliferation rate and a short doubling time, so it generally presents with a high tumor burden in advanced stages. General guidelines for treatment are as follows. Chemotherapy must be intensive, although adapted to tumor burden, combining several drugs, and given as pulse courses. The most frequently used drugs are cyclophosphamide (CPM), high-dose (HD) methotrexate (MTX), and cytarabine (ARA-C). Other effective drugs are doxorubicin, vincristine (VCR), VP16 (etoposide), ifosfamide, and corticosteroids. CNS prophylaxis is essential and is achieved by intrathecal injections of MTX and/or ARA-C, and by HD MTX ± HD ARA-C. CNS treatment is done with the same drugs at a higher dose. Cranial irradiation is thought to be ineffective in Burkitt and is therefore unnecessary. Treatment is of short duration, usually a few months. Relapses in Burkitt usually occur within the 1st year of treatment; therefore, a patient who is alive in first complete remission after 1 year can be considered as cured.

With the LMB protocols developed by the Societe Francaise d’Oncologie Pediatrique (SFOP) [12–14] and the Berlin-Frankfurt-Munster (BFM) protocols developed in Germany [15, 16], survival reaches an average of 90%. The lessons from these studies, but also from others [17–20], are:

1. Resected localized tumors (the minority) can be treated with very short treatment, some of them without any CNS prophylaxis [14, 16, 21–24].
2. The absence of tumor response at D7 after the pre-phase combining a low dose of VCR and CPM, and corticosteroids, indicates a bad prognosis and the need for intensifying treatment (LMB84 and LMB89 studies) [13, 14].
3. The introduction of HD ARA-C + VP16 increased the event-free survival (EFS) of patients with L3 ALL and who were CNS positive in the LMB86 and LMB89 group C studies (CYVE courses) [14] and that of patients with advanced stages in the BFM90 and BFM95 studies (course CC) [16, 25].
4. Treatment with HD MTX is very important in Burkitt. The more advanced the stage, the more treatment with HD MTX is important. The prognosis of stage III with high LDH and of any stage IV was greatly improved when MTX was increased from 0.5 to 5 g/m² in BFM86 and BFM90 [15, 16]. Results were also better in higher-risk patients when the infusion duration of HD MTX was longer (BFM95 study) [25].
5. Dose intensity during the 1st month is of great importance, as demonstrated in the FAB LMB96 study in which the outcome of the intermediate-risk patients was inferior when the second induction course was commenced more than 21 days after the first course [16, 26].

A few adolescents were included in these pediatric studies. There was a tendency in some studies toward an inferior EFS of patients older than 15 years [14, 27], but the numbers were too small to draw any definitive conclusions.

The LMB and the BFM regimens have been used in France and Germany, respectively, for young adult and older adult patients, but often with dose reduction of HD MTX because of poor tolerance of this drug in older patients. Does this explain the inferior results, or are they attributable to a different biology? It is interesting to note that the prognostic factors are the same in the LMB pediatric and adult studies: the absence of tumor response at Day 7 of therapy, LDH level, CNS involvement, and higher age. A study combining both children and adult databases will need to be performed.
to determine the prognosis of adolescents and young adults with Burkitt lymphoma and to determine the best course of management with either a pediatric or adult non-Hodgkin-lymphoma-based therapy.

Only two institutional studies (National Cancer Institute and Bologna) have addressed the question of outcome of adults and children treated in the same department with the same protocol. In a very small number of patients (41 and 21, respectively), they showed similar outcomes [17, 28].

Until further studies provide evidence to the contrary, adolescents and young adults probably should be treated with the pediatric regimens, without dose reductions.

One question concerns the use of rituximab in Burkitt. Some adult hematologists tend to use it systematically. There have been only a few case reports on the response in relapsed Burkitt [29, 30]. Currently, there is no published study demonstrating the benefit of rituximab in Burkitt. A study has just opened in France for adults comparing the LMB regimen with or without rituximab. A Children’s Oncology Group (COG) study investigating the safety and efficacy of rituximab in combination with FAB therapy has just opened.

### 9.7.2 Diffuse Large B-Cell Lymphoma

Depending on the country, DLBCL is included either in studies designed for Burkitt (LMB and BFM studies) [14, 16] or in studies designed for large cells in general (Pediatric Oncology Group, POG, studies) [31, 32]. In the LMB89 study, DLBCL represented 10% of all registered patients. As with Burkitt, they are treated according to initial resection and stage. The EFS is similar to that of Burkitt (Fig. 9.6), but it should be noted that the proportion of patients with advanced stages is lower than in Burkitt. However, by stage, EFS is not significantly different [33]. In the BFM90 study, the EFS of DLBCL is also similar to that of Burkitt. The criticism of such an approach is that too much CNS-directed therapy is given in DLBCL, in which the risk of CNS disease is lower than in Burkitt.

In a POG study, all advanced-stage large-cell lymphomas, by histology and/or immunophenotype, were treated with an APO (adriamycin + prednisone + vincristine)-based regimen. The addition of CPM did not change the outcome [32]. In another study, the addition of HD MTX and ARA-C was randomized. Results indicate a benefit to DLBCL, but not to ALCL [34].

In adults, recognized prognostic factors are age, IPI, LDH, stage, and to a lesser extent, number of extranodal sites and tumor size. Treatment is stratified according to these factors, including HD chemotherapy followed by autologous hematopoietic stem-cell rescue in poor-risk patients. Biologic characteristics may also have prognostic value, such as the presence of t(14;18)(q32;q21) involving bcl-2. Microarray studies have recognized two subtypes of DLBCL, the activated B-like and the germinal center-like ones, with different outcomes [35]. Overall therapeutic results in adults are not as satisfactory as in children. This raises the question of a different biology of DLBCL in children, where t(14;18)(q32;q21) is not seen, versus adults. What is the biology of adolescent and young adult DLBCL? Is it intermediate between that of adults and children, or closer to one or other of them?
The current main question is the addition of rituximab to chemotherapy. It was first shown in elderly patients with DLBCL that the addition of rituximab to CHOP (CPM + doxorubicin + VCR + prednisone) increased by 10–15% the complete response rate and the 3-year EFS and overall survival (OS) [36]. Recently, a European study in younger adults (18–59 years) also showed the benefit of adding rituximab to CHOP [37]. Consequently, it is now recommended that rituximab should be given with first-line chemotherapy in the treatment of adult DLBCL. Pediatricians who want to treat adolescents will have to take a position for their patients with DLBCL, knowing that their global results are better than in adults, that they use chemotherapy regimens different from CHOP, and that randomized studies addressing the question of rituximab are not possible due to the small number of patients.

One particular subtype of DLBCL is the primary mediastinal large B-cell lymphoma (PMLBCL), which has a different biology [38]. In the adult literature, there are controversies on their similarity or difference with other DLBCLs. The best therapeutic approach is not clearly defined, especially the potential role of radiotherapy. In the pediatric BFM and FAB LMB96 series, PMLCBL had a worse prognosis than other DLBCL, with an EFS of approximately 65–75% [39, 40]. Conversely, the Children's Cancer Group (CCG) claimed that the outcome of these lymphomas was better than for other DLBCLs [41]. In fact, the number of patients is small and there is a need to combine these data to find prognostic factors and to adapt therapy.

### 9.7.3 Anaplastic Large Cell Lymphoma

ALCL was first described as a distant clinicopathological entity in 1985 by Stein et al. [42] CD30 (Ki-1) expression was the hallmark feature that distinguished this lymphoma from the other forms of non-Hodgkin lymphoma. The characteristic t(2;5)(p23;q35) cytogenetic translocation was identified in 1989 to be associated with ALCL [43]. In 1994, Morris et al. cloned the translocation breakpoints of the nucleophosmin (NPM) gene on chromosome 5 and the anaplastic lymphoma kinase gene (ALK) on chromosome 2 [44]. The median age of presentation ranges between 17 and 50 years, with a bimodal age of distribution with a larger peak in the 20- to 30-year-old range and a smaller peak in the sixth and seventh decades of life [45–48]. ALK-positive ALCL tends to occur in the adolescent and young adult age range, whereas ALK-negative cases tend to occur in an older age group (43–61 years; Fig. 9.7) [49–51]. Cutaneous ALCL (C-ALCL) rarely occurs in the adolescent and young adult age group and is usually manifested in the sixth and seventh decades of life. There is a male predominance (6–7:1) in ALCL in the adolescent and young adult age group and patients tend to present with advanced-stage disease (stage III/IV) and extranodal involvement [51, 52]. Bone marrow involvement ranges between 11% (hematoxylin and eosin stains) and upwards to 34% when analyzed by immunohistochemistry [52, 53]. CNS involvement occurs in less than 3–5% of adolescent and young adult cases of ALCL [52].

#### 9.7.3.1 Biology/Pathology

ALCL is the least common form of adolescent non-Hodgkin lymphoma (<10%), is characterized by the expression of CD30 (Ki-1), and consists of two major histological subtypes, systemic (S-ALCL) and primary
C-ALCL [4]. ALCL is defined by large, pleomorphic, multinucleated cells or cells with eccentric horseshoe-shaped nuclei and abundant clear to basophilic cytoplasm with an area of eosinophilia near the nucleus (termed “hallmark cells”) [54]. These hallmark cells commonly resemble Reed-Sternberg cells (characteristic of Hodgkin lymphoma), although they tend to have less conspicuous nucleoli.

There are several morphologic variants of ALCL that have been identified in the REAL and WHO classifications [4, 5]. These variants include the common variety (75%), which is composed primarily of hallmark cells, the lymphohistiocytic variety (10%), which has a large number of benign histiocytes admixed with neoplastic cells, and the small-cell variety (10%), which is composed of small neoplastic cells and only scattered hallmark cells. Other (<5%) less well described variants include sarcomatoid, signet-ring, neutrophil-rich, and giant-cell variants [52, 55]. Neoplastic cells tend to infiltrate in a sinusoidal pattern in regional lymph nodes, mimicking metastatic disease, although diffuse effacement of nodes may also be demonstrated. There is a high propensity of S-ALCL to spread to extranodal tissues (skin, bone, soft tissues) either as the only sites of disease or, more commonly, in association with nodal disease [55].

C-ALCL is part of a spectrum of CD30-positive, T-cell lymphoproliferative disorders [52, 56, 57]. CD30-positive cutaneous lymphoproliferative disorders share overlapping pathologic and clinical features, and so diagnosis requires careful assessment of clinical, histologic, immunophenotypic, and genetic features. C-ALCL is a peripheral T-cell lymphoma of large, anaplastic, CD30-positive cells that is limited to the skin. C-ALCL usually presents as a solitary tumor, nodule, or papule that is composed of larger, pleomorphic cells that infiltrate the upper and deep dermis and extend into the subcutaneous tissues. Epidermal invasion is uncommon and surrounding inflammation is usually present [57].

Both S-ALCL and C-ALCL express CD30, as evidenced by immunohistochemistry [51]. The majority of ALCLs have been shown to be of the T-cell phenotype (CD2, CD3, CD5, CD7, CD45RO, CD43) or fail to stain with either T- or B-cell markers (null cell). Expression of cytotoxic antigens, such as TIA-1 or granzyme, and epithelial membrane antigen (EMA) is commonly observed in ALCL. ALK expression (P80) detects the fusion protein generated by translocations associated with S-ALCL. ALK staining is absent in C-ALCL, and, if observed, indicates the likelihood that systemic disease is present [58].

Most cases of S-ALCL and C-ALCL demonstrate T-cell receptor gene rearrangements, even when immunophenotypic analysis fails to demonstrate expression of T-cell antigens [52]. Cytogenetic and molecular analyses often demonstrate a characteristic genetic alteration involving the ALK locus on chromosome 2. Classically this is manifested as the t(2;5)(p23;q35) translocation, which includes a rearrangement of a nucleolar phosphoprotein gene (NPM1) adjacent to the ALK tyrosine kinase gene [44]. Less common translocations include translocation of ALK to partner genes on chromosomes 1, 2, 3, and 17, which also results in upregulation of ALK expression [59, 60]. The pattern of ALK staining is usually nuclear with or without cytoplasmic staining for t(2;5), and is only in the cytoplasm for many of the alternative translocations [52]. Greater than 90% of advanced adolescent and young adult cases of S-ALCL are associated with ALK translocations, which are commonly absent in C-ALCL and seen with lower frequency in adults with S-ALCL [52, 59, 60]. The presence of an ALK translocation or ALK protein expression, however, appears to be associated with a better prognosis in adults [52, 61].

### 9.7.3.2 Treatment/Management of S-ALCL

Optimal therapeutic approaches for limited S-ALCL have not been well defined [62]. In a recent report, children and adolescents with localized (stage I/II resected) ALCL with a median age of 10.5 years (0.8–17.3) achieved 100% EFS with 2 months of chemotherapy including dexamethasone, ifosfamide, MTX, ARA-C, etoposide, and prophylactic intrathecal therapy [63]. A 75% EFS has been reported in a small number of children and adolescents with localized CD30-positive large-cell lymphoma, presumably S-ALCL, who had a median age of 13 years (0.2–19.9 years) and were treated at St. Jude Children’s Research Hospital with three courses of CHOP, either with or without maintenance with 6-mercaptopurine
and MTX [64]. Similarly, in small numbers of children with limited-stage S-ALCL treated on United Kingdom Children’s Cancer Study Group studies 9001, 9002, and 9602, the 5-year EFS was 62% (39–82%) [65].

Poor-risk prognostic factors in childhood and adolescent advanced-disease S-ALCL that have been identified include organ involvement (liver, lung, spleen), mediastinal involvement, an elevated LDH, and/or disseminated skin disease [66, 67]. Adolescent and young adult patients with advanced-disease S-ALCL are commonly treated with anthracycline (doxorubicin)-containing chemotherapy regimens. The prognosis is significantly improved in patients with ALK+ expression and lower IPI scores [50, 51]. Gascoyne et al. demonstrated that the 5-year EFS and OS was 88% and 93%, respectively for ALK+ S-ALCL patients compared to 37% and 37%, respectively for ALK- S-ALCL patients (p<0.0001; Fig. 9.8) [50]. Falini et al. further demonstrated that the 10-year disease-free survival (DFS) and OS of ALK+ versus ALK- patients were significantly different (82±6% vs. 28±14%, p<0.0001) [51]. Similarly, patients with S-ALCL and an elevated IPI score ≥2 at diagnosis also had a significantly inferior outcome compared to patients with S-ALCL and IPI 0–1 (OS 41±5% vs. 94±5%, p<0.0001; Fig. 9.9) [51]. Furthermore, patients with CD56+ S-ALCL, ALK+ S-ALCL have an inferior prognosis compared to CD56-negative (ALK-negative) S-ALCL patients (5-year OS 70% vs. 35%, p<0.002) (Fig. 9.10) [68].
The use of CHOP-based therapies over a 6-month period in childhood S-ALCL has resulted in greater than 75% 3-year OS [64, 69]. Cooperative European studies using either BFM-NHL or SFOP HM89-91, and the POG study using an APO regimen (doxorubicin + prednisone + VCR) in children with advanced-disease S-ALCL have demonstrated a 65–75% 3- to 5-year EFS (Table 9.4) [63, 67, 70–73]. Children with advanced-disease S-ALCL treated on NHL-BFM 90 have achieved EFS rates of 76% after receiving short courses of intensive B-cell non-Hodgkin lymphoma therapy, stratified according to disease stage. The COG recently reported the results of a pilot study (CCG-5941) in children with stage III/IV S-ALCL [73]. CCG-5941 was a T-cell lymphoblastic protocol that was utilized as a pilot for advanced ALCL. Induction therapy consisted of VCR, prednisone, daunomycin, CPM, and l-asparaginase. Intensification phase followed with VCR, ARA-C, VP16, HD MTX, 6-thioguanine (6TG), and l-asparaginase. Maintenance therapy consisted of alternating pulses of: (1) CPM and 6TG; (2) VCR, prednisone, and doxorubicin; (3) VCR and HD MTX; and (4) ARA-C and VP16. The 3-year EFS and OS were 73±6% and 83±5%, respectively [73].

The treatment for adolescents and young adults with advanced-disease S-ALCL usually involves an anthracycline-containing adult, non-Hodgkin lymphoma chemotherapy regimen (Table 9.4). Gascoyne et al. reported on the results of 70 adults with S-ALCL (36 ALK-positive with a median age of 30 years) with anthracycline-containing regimens [50]. The 5-year OS and EFS for all 70 patients was 65% and 63%, respectively [50]. In the adolescent and young adult age group (median age 30 years) with ALK-positive S-ALCL, the 5-year OS was 79%, compared to 46% for ALK-negative patients (p<0.0003) [50]. Falini et al. similarly reported the results in 78 adults with S-ALCL (53 ALK-positive and 25 ALK-negative) treated on anthracycline-containing regimens [51]. OS was significantly improved in ALK-positive vs. ALK-negative patients (71±6 vs. 15±11%, p<0.0007; Table 9.4) [51]. A subpopulation of adult patients with advanced-disease S-ALCL has been treated with aggressive chemotherapy (F-MACHOP: 5-fluorouracil, MTX with leucovorin rescue, ARA-C, CPM, doxorubicin, VCR, and prednisone), involved-field radiotherapy, and mye-
loablative chemotherapy and autologous stem-cell transplantation [74]. Although the numbers are small (N=16; median age 35 years), the results are encouraging, with 100% DFS and OS [74]. It remains to be determined which subsets of newly diagnosed patients in the adolescent and young adult age group with ALK-positive disease require such aggressive and intensive therapy.

9.8 Lymphoblastic Lymphoma

LL was initially described as a distinct pathological entity by Sternberg in 1916 [75]. In 1975, Barcos and Lukes defined this pathological entity as “lymphoblastic lymphoma” because of its close morphologic similarity to blasts of acute lymphoblastic leukemia (ALL) [76]. LL is considered an aggressive form of non-Hodgkin lymphoma by the REAL and WHO classifications. The majority of LL cases (≥75%) express a T-cell lineage and the remainder express a pre-B or B-cell immunophenotype. The most typical cytogenetic abnormalities, especially of the T-cell immunophenotype, commonly include TCR gene rearrangement, including TCRα/β (14q11-13), TCRβ (7q32-36) and TCRγ (7p15). Other commonly abnormal rearranged genes that have been described in LL include TAL-1, TAL-2, TCL-1, TCL-2, TCL-3, HOX-11, RHOM-1, RHOM-2, LYL-1, TAN-1, LCK, PBX-1, and E2A among others. There is a high incidence of LL in children with a median age of onset at around 9 years [77–80], and more importantly, LL also has a peak incidence in the adolescent and young adult group (15–30 years) with a median onset of approximately 25 years of age [81, 83]. There is a predominant male to female ratio ranging in different studies from 2:1 to 3:1. LL tends to present most commonly as a mediastinal mass with variable CD20, CD22, HLA-Dr, and cytoplasmic immunoglobulin gene rearrangements and lacks evidence of somatic hypermutation [88]. Cytogenetic abnormalities are common (50–80%) in both B- and T-LL [81]. T-LL chromosomal breakpoints have included T-cell receptor (TCR) genes or specific oncogenes TCRα/δ (14q11), TCRβ (7q32-36), and TCRγ (7p15). Often the TCR enhancer or promoter elements are translocated and juxtaposed to putative transcription factors [81, 87]. Specific oncogenes associated with T-LL include TCL-1 (14q32), which is involved in t(7;14)(q35;q32) or t(14;14)(q11;q32), TCL-2 (11p13), which is involved in t(11;13)(p13;q11), TCL-3 (10q24), which is seen in t(8;14)(q24;q11), and TAL-1 (1p32), which is involved in t(1;14)(q32;q11).

LL has been well described in both the REAL and WHO classifications, including precursor T (and B) lymphoblastic lymphoma. Precursor B-cell disease predominates in ALL compared to most of the LLs that are of precursor T-cell origin (80–90% T cell vs. 10–20% B cell). Precursor T-cell LL tends to present as mediastinal or upper torso nodal masses, whereas precursor B-cell LL is more likely to present in skin, soft tissue, bone, tonsil, and peripheral lymph nodes [86].

The morphologic features of LL include diffuse or partial effacement of lymph nodes that usually infiltrate interfollicular zones with sparing of benign, reactive follicles. A starry-sky pattern derived from the presence of macrophages ingesting apoptotic debris occurs commonly. Cytologically, the neoplastic cells are indistinguishable from those seen in precursor B-cell or T-cell ALL. The cells have an immature, blast-like appearance with fine chromatin, inconspicuous or absent nucleoli, and scanty cytoplasm that ranges from pale to slightly basophilic in color, and most LL have a high proliferative rate [86].

Immature B- or T-lymphoid blasts express terminal deoxynucleotidyl transferase (TdT). T-LL commonly expresses CD1, CD2, CD5, and CD7 along with coexpression of CD4 and/or CD8. Occasionally, both CD4 and CD8 may be absent. CD10 is expressed in 15–40% of cases, and occasionally natural killer antigens such as CD57 or CD16 may be seen [86]. Precursor B-cell LL most often displays the immunophenotype of early pre-B or pre-B phenotypes (CD19, CD10, and TdT with variable CD20, CD22, HLA-Dr, and cytoplasmic immunoglobulin) [86].

T-LL will commonly display early T-cell gene rearrangements (TCRα, TCRγ, TCRδ, and/or TCRβ) [81, 87]. Precursor B-LL commonly demonstrates clonal immunoglobulin gene rearrangements and lacks evidence of somatic hypermutation [88]. Cytogenetic abnormalities are common (50–80%) in both B- and T-LL [81]. T-LL chromosomal breakpoints have included T-cell receptor (TCR) genes or specific oncogenes TCRα/δ (14q11), TCRβ (7q32-36), and TCRγ (7p15). Often the TCR enhancer or promoter elements are translocated and juxtaposed to putative transcription factors [81, 87]. Specific oncogenes associated with T-LL include TCL-1 (14q32), which is involved in t(7;14)(q35;q32) or t(14;14)(q11;q32), TCL-2 (11p13), which is involved in t(11;13)(p13;q11), TCL-3 (10q24), which is seen in t(8;14)(q24;q11), and TAL-1 (1p32), which is involved in t(1;14)(q32;q11).
9.8.2 Treatment and Management

Children with limited-disease LL, Murphy stages I and II, have a favorable prognosis with a long-term OS of 85–90%, but DFS rates of only 63–73%. The excellent OS rates have been attributed to effective salvage strategies for children who have relapsed after initial less-intensive therapies. Over the past 20 years, the need for local radiotherapy in children with LL, especially to the mediastinum, has been virtually eliminated [89]. Successful therapeutic approaches in children with LL have varied and have included CHOP with mercaptopurine and MTX maintenance (POG) [22, 89], LSA2L2 (Memorial Sloan-Kettering Cancer Center) [79], COMP (CPM + oncovin + MTX + prednisone; CCG) [23, 90], and modified LSA2L2 with the addition of HD MTX [91].

The treatment for limited-stage disease (I/II) LL in the adolescent and young adult group has been quite varied [91]. Most adolescent and young adult patients, with both limited stage and advanced stage (III/IV), have received similar treatment regardless of initial staging [91]. The probability of OS of limited-stage LL in the adolescent and young adult group varies from 40 to 60% [81]. Hoelzer et al. reported a 5-year OS rate for stage I/II LL in adolescents and young adults of 56±24% (Fig. 9.11) in the German ALL studies (GMALL) [83]. Few studies of LL in the adolescent and young adult age group have utilized involved-field radiotherapy, and most studies have utilized either CHOP, BFM, LSA2L2, BACOP (bleomycin + epidoxorubicin + CPM + VCR + prednisone), and/or M-BACOD (MTX + bleomycin + doxorubicin + CPM + VCR + dexamethasone)-type multiagent chemotherapy regimens.

The prognosis for children with advanced LL has improved significantly since the introduction of the 10-drug LSA2L2 regimen by Wollner et al. at MSKCC [91]. The CCG subsequently compared LSA2L2 with COMP in advanced LL in children [92]. The 5-year EFS for children with advanced-disease LL treated with LSA2L2 in comparison with COMP was significantly better (64% vs. 34%, p<0.001) [92]. Recent excellent results have also been demonstrated without the requirement of involved-field radiotherapy [80]. Treatment approaches for childhood advanced LL have varied, with many pediatric cooperative groups investigating ALL-based therapeutic regimens. An OS of 60–90% has been demonstrated using a variety of multiagent chemotherapy regimens ranging from 12 to 32 months of therapy (Table 9.5) [15, 77–81, 91–98]. More recently, excellent results (including a 90% EFS) have been demonstrated with the BFM NHL90 protocol, which utilizes HD MTX, dexamethasone, moderate doses of anthracyclines, and CPM, as well as prophylactic cranial radiation, with a treatment stratification based upon tumor response to induction therapy [80].

The treatment for advanced-stage (III/IV) LL in the adolescent and young adult group has also been varied. The probability of DFS in advanced-stage (III/IV) LL in the adolescent and young adult group has ranged from 30 to 60% [81]. Initial results with an LSA2L2-like regimen by Coleman et al. [99] and the Stanford group in 44 patients with LL yielded a 56% 3-year DFS. Morel et al. in a French cooperative series of studies utilizing CHOP, LNH-84, FRALLE, and LALA, demonstrated a 33–53% DFS in adolescent and young adult patients with advanced LL [100]. Zinzani et al. reported for the Italian cooperative studies an overall 56% 10-year DFS in patients with advanced LL treated on successive Italian studies (L17, L0288, L20) [101]. More recently,
Hoelzer et al., utilizing two German ALL protocols (GMALL89 and GMALL93), reported a 57% 3-year DFS in adolescent and young adult patients with advanced LL (Table 9.5) [83]. Finally, Thomas et al. at the MD Anderson Cancer Center have piloted the use of hyperfractionated-CVAD (CPM + doxorubicin + VCR + dexamethasone) in adolescents and young adults with advanced LL and demonstrated in early results a 3-year DFS of 72% [81]. In comparison with the results with treatment for advanced LL in children vs. adolescents and young adults, the outcome appears to be superior in children with the use of pediatric-designed treatment protocols (Table 9.5).

Additional approaches for advanced LL in the adolescent and young adult group have been the use of high-dose therapy and autologous or allogeneic stem-cell transplantation [81]. Bouabdallah et al. reported the results of allogeneic stem-cell transplantation (n=12; 11 underwent the procedure during their first complete remission, CR1) and autologous stem-cell transplantation (n=18; 16=CR1) in adolescent and young adult patients with advanced LL [102]. The overall 5-year EFS for all transplant patients was 66%,
compared to 33% in a similar group of patients not transplanted \((p<0.01; \text{Fig. } 9.12)\) \([102]\). The allogeneic subgroup had an OS of 78%, compared to 50% in the autologous transplant group \((p<0.06)\) \([102]\). Sweetenham et al. randomized adolescent and young adult patients (median age=26 years) with advanced LL in CR1 to high-dose therapy and autologous peripheral blood stem-cell transplantation (PBSCT) vs. continued chemotherapy \([103]\). The relapse-free survival was 55%, in the autologous PBSCT group compared with 24% in the chemotherapy group \((\text{Fig. } 9.13)\). In a retrospective analysis of autologous PBSCT vs. allogeneic stem-cell transplantation in patients with LL reported to the International Bone Marrow Transplant Registry and Autologous Blood and Marrow Transplant Registry, Levine et al. demonstrated that the relapse rate was significantly higher in the autologous vs. allogeneic subgroups \((34\% \text{ vs. } 56\%, \ p<0.004; \text{Fig. } 9.14)\) \([104]\). These results suggest that there may be an allogeneic graft vs. lymphoma effect in adolescent and young adult patients with advanced LL.

In summary, adolescent and young adult patients with advanced LL have benefited from the use of pediatric ALL-type chemotherapy regimens, long-term maintenance chemotherapy (12–24 months), aggressive intrathecal CNS prophylaxis, and high-dose therapy and stem-cell transplantation in selected patients in CR1 and responders in their first partial remission or in their second complete remission. Additional research is required to determine the molecular basis of adolescent and young adult LL, its relationship to pediatric LL, comparison to adolescent and young adult T-ALL, mechanisms of drug resistance, and the development of novel targeted therapeutic approaches.

### 9.9 Overall Survival

Overall 5-year survival rates of patients with all types of non-Hodgkin lymphoma by era during the past quarter century are shown in Fig. 9.15 as a function of age at diagnosis. Progress was most significant in children and young adolescents, with an increase from about 50% to over 89%. Among 15- to 29-year-olds, little progress was achieved until the 1990s, when the 5-year survival rate increased from about 55% to 65%.
Transient reductions in the 5-year survival rate noted among 15- to 44-year-olds in the late 1980s and early 1990s were related, at least in part, to the HIV/acquired immune deficiency syndrome (AIDS) epidemic in the United States.

For 25- to 45-year-olds in the United States with non-Burkitt, non-Hodgkin lymphoma, there was no improvement in 5-year survival rate when it was averaged over the past quarter century (Fig. 9.16). Both younger and older patients have had a much greater survival improvement. For Burkitt lymphoma, a similar lack of progress is evident (Fig. 9.16, inset), at least in comparison to children (the incidence of Burkitt lymphoma is too uncommon in older persons to allow for a comparison). Burkitt lymphoma has not been associated with HIV infection, and yet shows a similar adult survival improvement deficit. It thus is not likely that the HIV/AIDS era explains the relative lack of progress in lymphoma survival in young adults.

### 9.10 Conclusions

The incidence of non-Hodgkin lymphoma has increased in all age groups through to age 30 years, and in 20- to 29-year-olds, the increase has been dramatic, averaging 4–19% per year over 25 years. Follicular (nodular) and mantle cell lymphoma, virtually nonexistent before age 15 years, increases to represent 11% of all non-Hodgkin lymphomas among 25- to 29-year-olds. Males are far more likely than females to develop non-Hodgkin lymphoma, especially Burkitt lymphoma. For 15- to 29-year-olds with either Burkitt or non-Burkitt non-Hodgkin lymphoma, survival improvement has significantly lagged behind that achieved in children and older adults with the same diseases, a deficit that can not be attributed solely to the HIV era.

The biology, prognosis and best treatment regimen for adolescents and young adults with non-Hodgkin lymphoma is still currently largely unknown. Few comparative studies have been performed to determine if the genetics and/or biology of adolescent and young adult non-Hodgkin lymphoma are similar to those of childhood or adult non-Hodgkin lymphoma, or whether it is a distinct biological entity. The pediatric approach may be more beneficial for certain subtypes of adolescent and young adult non-Hodgkin lymphoma and with other subtypes there is little data to support either pediatric or adult approaches as being superior. Further research and collaboration with pedi-
iatric and adult oncology cooperative groups is required to improve our understanding of the biology and best treatment approach for this subset of adolescents and young adults with non-Hodgkin lymphoma.

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