Non-Hodgkin’s Lymphoma In Children And Adolescents

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Introduction/Epidemiology
Sixty percent of all childhood lymphomas have been classified as non-Hodgkin’s lymphoma, representing 3% of all childhood malignancies for children younger than 5 years, and 8-9% for children and adolescents 5-19 years of age. In the US, 750-800 cases of non-Hodgkin’s lymphoma are diagnosed annually in children and young adults younger than 20 years of age.\(^1\)\(^-\)\(^4\) There is also an increased incidence of non-Hodgkin’s lymphomas, especially B-cell lymphomas, in children with inherited and/or acquired immunodeficiencies.

The vast majority of childhood non-Hodgkin’s lymphomas are high-grade tumors with aggressive clinical behavior. Unlike adult non-Hodgkin’s lymphoma that is predominantly B-cell phenotype, paediatric lymphomas are almost equally divided between B- and T-cell neoplasms, and follicular or low grade lymphomas are distinctly uncommon.\(^5\)\(^-\)\(^8\) There are four major subtypes of childhood non-Hodgkin’s lymphoma: Burkitt lymphoma (classic and atypical Burkitt lymphoma), lymphoblastic lymphoma, diffuse large B-cell lymphoma (DLBCL) and anaplastic large cell lymphoma (ALCL). The distribution of these four main histologic subtypes includes approximately 40% Burkitt lymphoma, 30% lymphoblastic lymphoma, 20% diffuse large B-cell, and 10% anaplastic large cell lymphoma.

Additionally, correct staging is critically important at the time of diagnosis since most children present with advanced disease at diagnosis. The St. Jude’s Children’s Research Hospital staging classification, modified from the Ann Arbor system for Hodgkin’s disease, took into consideration the common presentations of childhood non-Hodgkin’s lymphoma including increased extranodal involvement, metastatic spread to the bone marrow and CNS, and noncontinuous spread of disease (Table 1A).\(^9\)

### Table 1A : St. Jude’s Staging Classification for Childhood Non-Hodgkin’s Lymphoma

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>A single tumor (extranodal) or single anatomic area (nodal) with the exclusion of mediastinum or abdomen</td>
<td>A single tumor (extranodal) with regional node involvement</td>
<td>Two single tumors (extranodal) on opposite sides of the diaphragm</td>
<td>Any of the above with initial CNS and/or bone marrow involvement (&lt;25% malignant cells)</td>
</tr>
<tr>
<td>Two or more nodal areas above and below the diaphragm</td>
<td>Two or more nodal areas on the same side of the diaphragm</td>
<td>Two or more nodal areas on the same side of the diaphragm</td>
<td></td>
</tr>
<tr>
<td>Two single (extranodal) tumors with or without regional node on the same side of the diaphragm</td>
<td>A primary gastrointestinal tract tumor with or without mesenteric nodes, grossly and completely excised</td>
<td>All of the primary intrathoracic tumors (mediastinal, pleural, thymic)</td>
<td></td>
</tr>
<tr>
<td>All extensive primary intra-abdominal disease</td>
<td>All paraspinal or epidural tumors, regardless of the other tumor site(s)</td>
<td>All paraspinal or epidural tumors, regardless of the other tumor site(s)</td>
<td></td>
</tr>
</tbody>
</table>

Limited-stage disease (stage I and II) is defined as one or two masses on one side of the diaphragm, whereas more advanced disease (stages III and IV) has been defined as either metastatic disease including the CNS and/or bone marrow disease or disease on both sides of the diaphragm and extensive intrathoracic and intra-abdominal disease. However, the St. Jude’s staging classification is unclear on the definition of extensive primary disease and considers all primary abdominal and thoracic tumors as extensive stage III disease, despite original surgical debulking, which may occur at diagnosis. Subsequently, a new French, American, and British (FAB) staging classification was developed (Table 1B) that better defines the staging of childhood B-large cell and Burkitt lymphoma of childhood. This staging classification was applied in the DLBCL and Burkitt lymphoma international study (LMB-FAB) within the Children’s Cancer Group (CCG), United Kingdom Children’s Cancer Study Group (UKCCSG), and the Societe Francaise d’Oncologie Pediatrique (SFOP) study groups.

**Table 1B : FAB* Staging System for Childhood B-Large and Burkitt Lymphoma**

<table>
<thead>
<tr>
<th>Group A</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Completely resected Stage I (St. Jude)</td>
<td>Complete resected abdominal Stage II (St. Jude)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients not eligible for Group A or Group C</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group C</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CNS involvement† and/or bone marrow involvement (&gt;25% blasts)</td>
<td></td>
</tr>
</tbody>
</table>

*FAB: French, American, British
†CNS: Any L3 blast, cranial nerve palsy or compression, intracerebral mass, and/or parameningeal compression

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**Diffuse Large B-Cell Lymphoma (DLBCL)**

**Treatment and prognosis of Limited Stage Childhood and Adolescent Diffuse Large B-Cell Lymphoma (DLBCL)**

Children and adolescents with limited disease DLBCL, either St. Jude’s stage I and II, CCG limited stage, or FAB group A, have an excellent prognosis with an estimated 5-year event-free survival (EFS) of 90-95%. Over the past 10-15 years, there has been significant progress in reducing the amount of therapy required for limited stage childhood DLBCL and eliminating the need for radiotherapy. While surgery plays a major role in the diagnosis and/or complete resection of limited DLLCL, multiagent chemotherapy in large part accounts for the excellent survival recently reported. The length of treatment for childhood limited stage DLBCL currently ranges between 6 weeks to 6 months of multiagent chemotherapy. Current chemotherapy regimens that have been successfully utilized in this clinical setting include COMP (CCG and POG) (3-6 months), COPAD (x 6 weeks) (FAB), or cyclophosphamide and prednisone (CP) followed by dexamethasone/ifosfamide/Ara-C/VP-16/methotrexate and dexamethasone/cyclophosphamide/methotrexate/doxorubicin (12 weeks) (BFM).

**Treatment and Prognosis of Childhood and Adolescent Advanced DLBCL**

The prognosis of advanced childhood and adolescent DLBCL has improved significantly over the past decade. The chemotherapy combinations that have been used for advanced large B-cell (non-anaplastic) childhood lymphoma include “APO” + Ara-C/VP-16 (POG), “Orange” (CCG), LMB (FAB) and BFM-NHL (BFM). The recent use, however, of short but intense chemotherapy such as FAB/LMB 96 (FAB), Orange (CCG) or BFM NHL90 (BFM) has now resulted in a greater than 90% 3-year survival rate in children with advanced B-large cell (non-anaplastic) lymphoma. The CCG hybrid regimen “Orange”, which consists of CHOP-based induction, VP-16/ifosfamide intensification and DECAL intensification and a similar maintenance phase with a slight decrease in intensity, results in a 90% overall survival rate in children and adolescents with advanced
Similarly, Patte et al, utilizing an FAB/LMB-type regimen of COP reduction, COPADM intensification, and CYM consolidation in children and adolescents with advanced DLBCL, demonstrated a 90% 5-year EFS. Reiter et al, utilizing a BFM approach of CP, ifosfamide, methotrexate, dexamethasone, Ara-C, VP-16 and cytarabine/methotrexate/cyclophosphamide/dexamethasone/doxorubicin, demonstrated a 95% 3-year EFS. All three of the above advanced B-LCL approaches have utilized a chemotherapy regimen designed to treat Burkitt (classic and atypical) lymphoma. Laver et al, however, utilizing an approach more designed for LCL and not Burkitt lymphoma (APO + VP-16/Ara-C), only demonstrated a 78% EFS with this approach. Patients with advanced DLBCL that still have a somewhat inferior outcome include those with a primary mediastinal DLBCL and patients with bulky tumors (stage III) with elevated LDH levels.

**Burkitt Lymphoma in Children and Adolescents**

**Treatment and Prognosis in Limited Stage Childhood and Adolescent Burkitt Lymphoma (BL)**

Similar to limited stage DLBCL, children and adolescents with limited stage, either St. Jude stage I and stage II, CCG limited stage, or FAB group A, with Burkitt lymphoma have a superb prognosis with an estimated five-year EFS of 90-95%. Similar to limited stage childhood DLBCL, the requirement for radiotherapy has been eliminated over the past decade as a requirement for treatment in children with limited stage Burkitt lymphoma. With minimal chemotherapy (range 6 weeks to 6 months), the prognosis is excellent, ranging between 90-95% five-year EFS. There are several multiagent chemotherapy regimens that have been utilized by a variety of paediatric cooperative groups that have resulted in this excellent outcome, including COPAD (6 weeks) (FAB), COMP (3-6 months) (CCG and POG), or cyclophosphamide and prednisone (CP) followed by dexamethasone/ifosfamide/Ara-C/VP-16/methotrexate and dexamethasone/cyclophosphamide/methotrexate/doxorubicin (BFM) (12 weeks).

**Treatment and Prognosis of Childhood and Adolescent Advanced Burkitt Lymphoma**

The most dramatic advances in the cure of childhood non-Hodgkin's lymphoma have been the significant improvement in disease-free and overall survival of advanced Burkitt lymphoma over the past twenty years. In four consecutive Children's Cancer Group (CCG) studies from 1977 through 1995, there has been a steady improvement in the 3-year disease-free survival in children and adolescents with advanced Burkitt lymphoma. Patte et al, utilizing an LMB-type regimen of COP reduction, COPADM intensification, and CYVE consolidation in children and adolescents with advanced Burkitt lymphoma, recently demonstrated a 90% 3-year disease-free survival. Reiter et al, utilizing a BFM approach (BFM95) (R2 and R3) regimens in children with advanced Burkitt lymphoma, reported an estimated 4-year event-free survival of 89% and 74% for bulky disease B-NHL and B-ALL, respectively. Most recently, the international FAB/LMB 96 study has demonstrated that with standard FAB therapy, children and adolescents with bone marrow involvement have a >90% 3-year EFS and patients with CNS involvement have a 71% 3-year EFS with short and intensive chemotherapy.

Children and adolescents with bone marrow and/or CNS involvement have an inferior outcome if they have a non response to reduction chemotherapy with COP or have combined bone marrow and CNS disease. Although elevated LDH is still associated with being a poor-risk factor for both stage III BL and DLBCL, LDH has not been shown to be prognostically important in patients with BM and/or CNS disease. Furthermore, in the most recent FAB/LMB 96 and BFM NHL 95 studies, both studies have demonstrated that cranial irradiation can be eliminated in patients with CNS positive disease with the substitution of more aggressive high-dose methotrexate and additional intrathecal chemotherapy.

**Lymphoblastic Lymphoma (LBL)**

Encompassing 20-25% of childhood NHL, LBL is morphologically indistinguishable from acute lymphoblastic leukemia (ALL). Approximately
80% of LBL are of immature T cell phenotype and 15-20% precursor B lineage. T-LBL most commonly presents with advanced stage disease, while precursor-B LBL more often presents with localized disease and may present at unusual sites such as skin or bone or with disease below the diaphragm.

T-LBL is derived from thymic T cells, expressing the pan-T antigen CD7. Other antigens which may be expressed, depending on the stage of differentiation, are CD2, CD3, CD45RO, as well as other markers of immature T cells such as CD4 and CD8 double-positivity or double-negativity. Precursor B-cell LL expresses the childhood ALL phenotype (CD10, CD19, CD22, HLA-DR). Many different translocations may be seen in T-LL, usually involving translocation of a protooncogene to one of the T-cell receptor (TCR) genes, a/d on chromosome 14q11.2, less commonly b on chromosome 7q35 or TCR gamma 7p14-p15, resulting in aberrant expression of the oncogene. The most common translocations are t(11;14) (p13;q11) in 7%, t(10;14) (q24;q11) in 5% and t(1;14) (p32-p34;q11) in 3% of cases. Other common abnormalities involve the tal-1 gene on chromosome 1, found to be overexpressed in 30% of T-leukemia/lymphoma. Genetic alterations that result in tal-1 activation or novel TAL-1 protein interactions are seen in the majority of T-cell ALL and NHL. Finally, inactivation of the multitumor suppression gene (mts-1), located on chromosome 9p21, may be the most common genetic defect found in T-cell leukemia/lymphoma.

### Therapy of T-Lymphoblastic lymphoma

#### Localized LBL

Induction therapy results in a 95% CR rate in the 15% of early stage NHL patients with localized LBL, however, this subgroup is prone to late relapses. In the POG 9219 trial, with 9 weeks induction therapy and 6 months of continuation therapy (6-mercaptopurine [6-MP] and low dose methotrexate [MTX]), the EFS was only 60%, the majority of patients relapsed in the bone marrow. Most were salvaged, giving an overall survival (OS) of >90% at 5 years. In contrast, the BFM group used more intensive therapy and achieved an EFS of 90% using the standard arm of the BFM T-cell protocol (standard BFM induction, consolidation phase consisting of 4 doses of high dose [5 gm/m²] MTX and maintenance therapy given for 2 years). No reinduction therapy or local or cranial radiation was given for stage I and II patients. A recently-opened COG study will attempt to confirm the BFM results. If successful, this strategy will increase the risk of therapy-related morbidity, but will obviate the need for intensive salvage therapy for 40% of the patients with localized LL.

#### Advanced stage LBL

Advanced stage LBL has been shown to respond best to protocols designed for acute lymphoblastic leukemia (ALL). Local radiation therapy, although effective, results in significant late risks particularly, when applied to the mediastinum, and is unnecessary if adequate chemotherapy is given. The results of the various chemo-therapeutic regimens are shown in Table 2.

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### Table 2: Outcome for Patients with Lymphoblastic Lymphoma

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Number</th>
<th>Stage</th>
<th>EFS (%)</th>
<th>Follow-up (mo)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSA2L2 / ADCOMP</td>
<td>281</td>
<td>II/III/IV</td>
<td>74/64</td>
<td>60</td>
<td>(37)</td>
</tr>
<tr>
<td>POG 8704</td>
<td>218</td>
<td>III/IV</td>
<td>67</td>
<td>60</td>
<td>(32)</td>
</tr>
<tr>
<td>LMT 81</td>
<td>76</td>
<td>III/IV</td>
<td>76</td>
<td>57</td>
<td>(38)</td>
</tr>
<tr>
<td>UKCCSG</td>
<td>59</td>
<td>III/IV</td>
<td>65</td>
<td>60</td>
<td>(36)</td>
</tr>
<tr>
<td>BFM90</td>
<td>82/19</td>
<td>III/IV</td>
<td>90+3 95+5</td>
<td>60</td>
<td>(30)</td>
</tr>
</tbody>
</table>
Results of POG 8704 in which both T-ALL and T-LBL patients, randomized to receive L’asparaginase 25,000 u/m² weekly x20 during maintenance, did significantly better than the no-L’asparaginase group, as well as preliminary results of the BFM-95 study suggest that this drug is important in therapy of T-cell disease. In the BFM studies, the results were better for males, with an EFS of 87% compared to 77% in females. The worst prognosis was seen in adolescent females, with a pEFS of 51% ± 19%. Other risk factors for failure were evaluated and only the presence of “B” symptoms was found to be prognostic (EFS of 74% vs 87% in patients without symptoms). Despite an earlier study in which incomplete tumor resolution at day 60 of therapy produced a RR for relapse of 3.55, incomplete resolution at day 33 or the end of induction did not predict for failure in the BFM-90 study. Reiter also evaluated the need for cranial irradiation (CRT). 357 patients received CRT, 52 (15%) relapsed of whom 8 (2%) had CNS involvement, compared to 410 patients without CRT, 118 of whom relapsed, 18 (4%) with CNS disease. In CCG-502 CRT was eliminated, with an incidence of isolated CNS relapse of only 2%, and the SFOP study also suggested that CRT can successfully be replaced by intensive chemotherapy including high dose MTX. The open COG study and BFM-95, do not give CRT for CNS-negative T-LBL patients, but the studies are being closely watched. Finally most studies gave 24 months of therapy for T-LBL but in the BFM-90 study all relapses occurred by 12 months from diagnosis, suggesting that therapy duration can safely be shortened to 18 months.

Thus the cooperative group studies suggest that ALL type therapy is effective for T-LBL. It appears that L’asparaginase is an important drug, and several, but not all, studies also suggest that high dose MTX results in a survival advantage. The studies further suggest that dose intensity in the first 4 weeks of therapy may be important and that cranial radiation may not be necessary if either high dose MTX and/or intensive intrathecal therapy is given. Similarly local radiation therapy is not indicated if adequate chemotherapy is given. The SFOP and BFM studies suggest that even in patients with testicular disease at diagnosis, testicular radiation is only indicated for residual disease after high-dose MTX. It appears that more than 50% of the relapses are local, often mediastinal and that salvage after relapse is poor.

B-Precursor LBL
Approximately 20% of LBL express B-cell markers. Nuclear TdT+ and lack of surface Ig expression are decisive parameters in differentiating B-LBL from mature B-cell neoplasms. Because of small patient numbers, the correct treatment for B-lineage LL has not been clearly defined. Twenty-seven children with precursor B-cell LL were treated on the BFM 86 and BFM 90 NHL trials, 21 on ALL-type therapy with 2/21 relapses, 6 on Burkitt-type therapy with 3 of 6 relapsing including 2 with localized disease; all 3 were salvaged with ALL-type therapy, suggesting that patients with B-lineage LL should be treated as ALL for a therapy duration of 18-24 months. The pEFS for the total group was 0.73 (SE 0.10) and pOS 92% (SE 0.05) at 10 years, correlating well with the results of a recent review which found 98 reported patients, 64% <18 years old. Approximately 75% had skin disease (with or without adjacent nodal disease), lymph node, bone, head and neck, and retroperitoneum. Mediastinal disease was uncommon. Five patients (4.8%) had CNS disease. Eighty-one patients had long term follow up data, 60/81 (74%) are disease free (median. 28 months). Thus with ALL type therapy, the majority of patients have a good outcome.

Anaplastic Large Cell Lymphoma (ALCL)
ALCL represents 10%-15% of paediatric NHL. Approximately 65% of ALCL are of T-cell phenotype and 35% null cell. B-cell lymphomas with anaplastic histology have been moved to the category of diffuse large B-cell lymphomas. ALCL cells react with antibody to CD30, epithelial membrane antigen (EMA) is generally positive, and CD25 (IL2-R) is often expressed, other markers are variable. T-ALCL cells usually express an aberrant T-cell phenotype, (usually activated helper T-cell phenotype (CD4+), lacking one or more pan-T cell antigens, usually CD3). Clusterin, a highly conserved glycoprotein, is found in the majority of ALCL, allowing differentiation from Hodgkins disease. The majority of childhood ALCL
show a characteristic translocation t(2;5)(p23;q35) relocating a promoter sequence of the nucleolar phosphoprotein \( (\text{npm}) \) encoding gene on 5q35 to the anaplastic lymphoma kinase gene, \( \text{alk} \) on 2p23, resulting in production of the fusion protein ALK, a tyrosine kinase. Pleiotrophin (PTN), the ligand that activates ALK, has been shown to have a role in tumorigenesis in nude mice.\(^{43} \) ALK can be recognised immunohistochemically on fixed tissue, using an anti-ALK1 monoclonal antibody. NPM-ALK is found in \( \sim 80\% \) of ALK pos ALCL, the remainder due to variant translocations; at least 8 have been described to date. NPM-ALK has a characteristic nuclear and cytoplasmic distribution pattern, thus the variant ALK fusion proteins, most of which are cytoplasmic in distribution, can be easily identified. A minority of primary cutaneous ALCL (PCALCL) and Hodgkins (HL) show NPM-ALK transcripts but no detectable protein, thus detection of ALK reliably differentiates ALK+ ALCL from other CD30+ tumors such as LYP, HL and PCALCL.\(^{42} \) Survivin, a target of the STAT3 pathway, is activated in approximately 50% of ALCL and may predict unfavorable prognosis, independent of ALK status, at least in adult patients.\(^{44,45} \) ALCL commonly involves unusual sites such as bone, skin and peripheral nodes and may present with manifestations such as diffuse pulmonary disease not common in other lymphomas. It may present with a systemic or primarily cutaneous distribution. PCALCL is more indolent than systemic ALCL and has a better prognosis. Despite the often-widespread nature of ALCL, involvement of CNS and marrow are uncommon.\(^{46} \)

### Therapy of Systemic ALCL

For advanced-stage ALCL, the major study groups have used very different strategies, varying from short-pulse chemotherapy (BFM), to more prolonged chemotherapy derived from T-cell protocols (SFOP, CCG), to inclusion on protocols designed for all large cell lymphomas (POG). The results of the various protocols are shown in Table 3.

Duration of therapy for advanced ALCL varied from 4-5 months (BFM-90) to 7-8 months (SFOP) to 12 months (POG9315). In the BFM studies, relapses tended to occur with a mean time of 8 months after achieving remission.\(^{47} \) Le Deley evaluated risk factors for ALCL in the combined BFM, SFOP and UKCCSG studies and found that in multivariate analysis of 235 patients with a median follow up of 47 months, mediastinal involvement (\( p=0.004 \)), lung, spleen and/or hepatic disease (\( p=0.006 \)) and skin lesions (\( p=0.02 \)) were associated with a significantly poorer outcome.\(^{48} \) Based on this, two risk groups were delineated: standard (EFS 87%, OS 92%), and high risk (skin, mediastinal and/or visceral disease) (EFS 61%,OS 67%).

### Table 3 : Treatment Outcome for Patients with ALCL

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Number</th>
<th>Stage</th>
<th>EFS (%)</th>
<th>Med Follow-up (Mo)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFM 90</td>
<td>8</td>
<td>I</td>
<td>100</td>
<td>30</td>
<td>(47)</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>II</td>
<td>79+9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>III</td>
<td>74+6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>IV</td>
<td>50+20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFOP-LM 89, 91</td>
<td>82</td>
<td>I/II/III/IV</td>
<td>94/55</td>
<td>49</td>
<td>(49)</td>
</tr>
<tr>
<td>LSA2L2/LSA4</td>
<td>19</td>
<td>III/IV</td>
<td>56</td>
<td>60</td>
<td>(50)</td>
</tr>
<tr>
<td>UKCCSG</td>
<td>72</td>
<td>III/IV</td>
<td>59</td>
<td>51</td>
<td>(51)</td>
</tr>
<tr>
<td>CCG-5941</td>
<td>86</td>
<td>III/IV</td>
<td>78+5</td>
<td>16</td>
<td>(52)</td>
</tr>
<tr>
<td>POG 9315</td>
<td>86</td>
<td>III/IV</td>
<td>71.8+6</td>
<td>48</td>
<td>(53)</td>
</tr>
</tbody>
</table>
In summary therefore, the cooperative trials suggest that children with T-cell/null-cell ALCL can be successfully treated with strategies varying from short-pulse intensive chemotherapy to longer less intensive, non-alkylator protocols. CNS and bone marrow involvement is unusual in ALCL and intermediate- or high-dose MTX with (BFM) or without intrathecal therapy (SFOP) or even IT therapy alone (COG) effectively prevents CNS relapse without CRT. Risk factors for relapse include the presence of mediastinal, visceral and/or skin involvement and possibly “B” symptoms. Current study group protocols are investigating the efficacy of the addition of weekly vinblastine to standard chemotherapy for ALCL, based on the successful SFOP salvage therapy results.

Summary
The prognosis for children and adolescents with non-Hodgkin’s lymphoma, both with limited and advanced stage disease, has improved significantly over the past two decades. Except for rare subtypes, the chance of being alive and disease free at five years for limited and advanced stage disease B-NHL is 95% and 80%, respectively. The prognosis for advanced lymphoblastic non-Hodgkin’s lymphoma in children and adolescents has now increased to over 85% survival. The prognosis, however, for the most advanced childhood and adolescent ALCL is still less than 70% at 7-year follow-up. The improved outlook for childhood non-Hodgkin’s lymphoma, however, has not come without a certain price. The use of short but intense chemotherapy, especially in B-NHL, has resulted in long hospitalizations and severe hematopoietic and non-hematopoietic toxicity. Furthermore, long-term complications or late effects, such as sterility, cardiomyopathy, and secondary malignancies, still occur following the use of the aggressive multiagent chemotherapy in children and adolescents with advanced non-Hodgkin’s lymphoma.

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