Non-Hodgkin lymphoma across the pediatric and adolescent and young adult age spectrum

John T. Sandlund[1,2] and Mike G. Martin[3,4]

[1]Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN; [2]Department of Pediatrics, University of Tennessee College of Medicine, Memphis TN; [3]Department of Medicine, University of Tennessee College of Medicine, Memphis, TN; and [4]The West Cancer Center, Memphis TN

The non-Hodgkin lymphomas (NHLs) occurring in children and adolescents and young adults (AYA) are characterized by various age-related differences in tumor biology and survival. Children generally present with high-grade lymphomas, such as Burkitt lymphoma, diffuse large B-cell lymphoma, lymphoblastic lymphoma, and anaplastic large cell lymphoma, whereas low-grade histologic subtypes, such as follicular lymphoma, occur more frequently with increasing age. Treatment outcome for children with NHL is generally superior to that observed in adults. Factors contributing to this discrepancy include psychosocial factors, patient factors, and differences in tumor biology and therapy. These factors will be reviewed, with particular attention to the biological features of diffuse large B-cell lymphoma and anaplastic large cell lymphoma and corresponding therapeutic challenges. Novel targeting agents have been developed, which have been shown to be active in some patients. There is clearly a need for treatment protocols with eligibility criteria that cover the full span of the pediatric and AYA age range and that incorporate detailed molecular characterization of the tumors.

Learning Objectives

- To describe age-related biological differences in NHL occurring in the pediatric and AYA population (ages 1-39)
- To describe current treatment approaches for NHL in children and adults, and to identify ongoing challenges in determining optimal treatment approach for the AYA population

Introduction

Define NHL with demographics (SEER)

The non-Hodgkin lymphomas (NHLs) are characterized by various age-related differences in clinical presentation, biology, and outcome.[1,2] Children younger than 16 years of age are defined as the "pediatric" group, whereas patients whose age is within the 16 to 39 range, are considered the "adolescent and young adult (AYA)" group.[3,4] The frequency of newly diagnosed NHL increases with increasing age. The annual frequency in the US (SEER database) for those in the pediatric, AYA, and older adult (>40) age groups is 0.5 to 1.2 per 100 000, 1.8 to 7.2 per 100 000, and 10.5 to 116.4 per 100 000, respectively.[3] The treatment outcomes for those with newly diagnosed NHL in the pediatric age group are generally better than that for the AYA and older age groups.[3-8] There are various reasons for the age-associated discrepant treatment results, and these challenges must be carefully considered as initiatives are developed to improve outcomes. Some of these challenges pertain to sociologic and psychosocial aspects of the individual age groups, whereas others are more directly related to the patient's general medical condition and specific biological NHL subtype.[3,4]

Sociological and Psychosocial challenges. Those in the pediatric age group generally have a parent or guardian advocating for their care, and in cases where this is lacking, the multidisciplinary medical team (social worker, child life, nursing, pharmacy, and medical staff) in the local children's hospital often makes extra efforts to ensure compliance with the chemotherapy plan and delivery of appropriate supportive care for this vulnerable population. Those in the AYA group face some unique challenges as they transition to relative independence. Risk factors that may affect the AYA age group include difficulty to secure insurance, inconsistent medical care with delay in diagnosis, poor compliance with medication, low rates of enrollment in clinical trials, and less structured supportive care.[3] In this regard, the AYA population may in some cases also be considered at potentially higher risk or more vulnerable.[3,9] Programs to help address these needs have been implemented by the National Cancer Institute and the American Society of Clinical Oncology.[3] The most promising new treatment approaches will not be successful if the psychosocial infrastructure is not securely in place to deliver them.

Patient factors. There are certain age-associated patient/host factors that can influence treatment outcome. The International Prognostic Index (IPI), which includes the patient's performance status, has been shown to have significant prognostic value for adults with NHL.[10] Although components of the IPI, such as lactate dehydrogenase (LDH), may have prognostic significance in children, performance status is not routinely used in planning therapy for those with newly diagnosed NHL in the pediatric age group. However, there are some inherited immunodeficiency conditions, such as ataxia-telangiectasia and X-linked lymphoproliferative syndrome, where specific treatment modifications need to be incorporated.

Age-related pharmacokinetic challenges must be considered in treatment planning. In this regard, drug clearance may vary with age and the maximum tolerated dose for many cancer agents is higher in younger patients.[11] An example of this is the inability of older patients

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with aggressive NHL to tolerate dose-intensification with CHOEP in NHL-B2, whereas the addition of etoposide improved outcomes in younger patients.[12,13] Moreover, drug-drug interactions may influence clearance and metabolism of certain chemotherapy agents.[14]

Tumor subtype and biology. The spectrum of NHL subtypes varies with age (Figure 1).[4] The NHL subtypes occurring in children younger than 16 years of age are primarily high-grade tumors comprising BL, DLBCL, lymphoblastic lymphoma (LL), and ALCL.[15] Low-grade B-cell lymphomas, such as FL and marginal zone B-cell lymphomas (MZBCL), are much less common, but increase in frequency with increasing age.[1,4,15] Among histologic subtypes, biological differences between age groups have been described, which have significant impact on treatment approach and outcome.[16-20]

The remainder of this review will deal with age-associated tumor biology and treatment outcome differences, with an emphasis on DLBCL and ALCL, where the greatest challenges lie.

High-grade mature B-cell lymphomas

Diffuse large B-cell lymphoma

Biology. The DLBCLs are mature B-cell neoplasms characterized by the expression of surface immunoglobulin (sIg) and B cell–associated surface markers (CD19, CD20, CD22, and CD79a).[15] There are 2 main categories of DLBCL, which include the germinal center (GCB) and activated B-cell (ABC) subtypes. This biological distinction among patients with DLBCL appears to vary with age. Younger patients are more likely to have GCB disease than adults (age 0-9 years 95% GCB, 10-19 years 80% GCB, adults 42% GCB, χ^2 2-sided P value $< .0001$).[21,22] GCB DLBCL has been consistently associated with improved outcomes over non-GCB disease.[22,23]

BCL2 expression generally increases with age and is associated with inferior outcomes in DLBCL.[24] The adverse risk associated with the ABC subtype is likely in part secondary to the upregulation of downstream targets of NF-κB, which include BCL-2 and cyclin D2.[4]

Various genetic abnormalities have been detected in cases of DLBCL. 8q24 *MYC* rearrangements may be present and have been associated with a poorer prognosis in some studies.[20] Other reported abnormalities include the t(14;18)(q32;q21) and 3q27 *BCL6* rearrangements; however, these are uncommon in pediatric cases.[2,25] *IRF4* oncogene rearrangements, which have been identified in a small subset of B-NHLs with a distinct immunophenotype from the GCB and ABC subtypes of DLBCL, occur more commonly in those younger than 18 years of age.[20,26]

Recurrent translocations involving *BCL-6*, *BCL-2*, and *MYC* are of particular interest because of the associated adverse risk. Double-hit lymphomas (DHLs), which are associated with a very poor prognosis in adults, are DLBCLs that contain translocations involving any 2 of these translocations (*MYC*/*BCL2*, *MYC*/*BCL6*, *MYC*/*BCL2*/*BCL6*). DHLs are associated with dismal outcomes and are largely restricted to adults with GCB-DLBCL as DHLs are incredibly rare in the pediatric population.[20,27,28] The spectrum of oncogenic mechanisms and therapeutic targets for the DLBCLs, which vary according to the molecular subtype (ABC, GCB, and PMLBCL [primary mediastinal large B-cell lymphoma]), have been extensively reviewed (Table 1).[19]

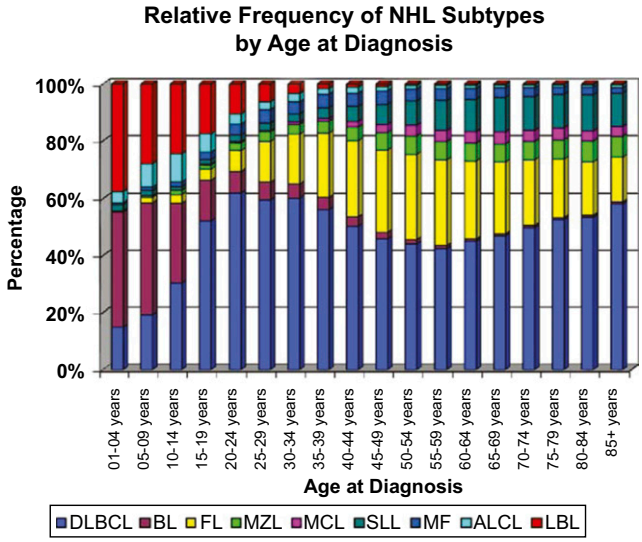

Figure 1. ALCL, anaplastic large-cell lymphoma; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; LBL, lymphoblastic lymphoma; MCL, mantle cell lymphoma; MF, mycosis fungoides; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma. Reprinted with permission from Jaglowski et al.[4]

The BFM (Berlin-Frankfurt-Meunster) study of pediatric DLBCL confirmed that the majority of cases have a GCB phenotype. They also reported a stronger association with CD10 and BCL-6 expression in children compared with adult cases; however, there did not appear to be age-related differences in expression of BCL-2 or MUM-1.[4,25] The International FAB (French-American-British) study also demonstrated a predominance of the GCB phenotype among cases of pediatric DLBCL.[21] They reported that pediatric cases have a higher proliferative rate and greater MYC expression, but are generally not associated with BCL-2 overexpression.[21] The superior outcome for children with DLBCL had been thought to be secondary to the predominance of the GCB subtype in children; however, there does not appear to be adverse risk associated with the ABC phenotype in the pediatric population.[20] The inability to demonstrate an associated adverse risk for ABC cases in children may simply be a consequence of the small number of ABC cases in this age group, or may reflect age-related differences in treatment.

Treatment

Pediatric. Over the past 15 to 20 years, most children with DLBCL have been treated with regimens designed for BL, resulting in what appear to be superior outcomes compared with CHOP-based approaches used in earlier treatment eras. For example, a 4-year event-free survival (EFS) of 92% was reported for children with DLBCL (excluding those with primary mediastinal large B-cell lymphoma, PMLBCL) compared with 93% for those with BL treated with the very successful LMB-96 regimen for children with BL and other high-grade mature B-cell lymphomas (Group B, age range: 2.5-20.5 years).[29-31] A similar observation was made in the BFM mature B-cell study in which children with DLBCL were treated with a contemporary regimen designed for those with BL (all patients <18 years of age).[32] Efforts to further improve outcomes for those with DLBCL have featured the incorporation of rituximab into frontline therapy. The COG performed a pilot study in which 6 doses of rituximab were incorporated into an LMB-96 backbone.[33,34] The feasibility results of this study led to an international B-NHL protocol for children with high-grade mature B-cell lymphomas (including

Table 1. Non-Hodgkin lymphoma: oncogenic mechanisms and therapeutic target

Lymphoma Subtype	Pathways altered	Targeted Agents	Clinical trials	Age of patients eligible (years)
DLBCL	Programmed death-1	Pembrolizumab	NCT02541565	18+
	CD79b	Polatuzumab vedotin	NCT01992653	60-80
	Programmed death-1 plus BCR activation	Nivolumab plus ibrutinib	NCT02329847	18+
	CD20	Obinutuzmab	NCT02670317	18-60
	BCL-2	Venetoclax	NCT02055820	18+
	NK cell activation	Lenalidomide	NCT00670358	18-120
	CD30	Brentuximab vedotin	NCT01925612	18+
GCB	BCL-2 translocation			
	EZH2 mutations	CUDC-907	NCT01742988	18+
	PTEN deletions			
nonGCB	NF-κB activation	Bortezomib	NCT01848132	18-70
	CARD11 mutations			
	BCR mutations	Ibrutinib	NCT02219737	18+
	MYD88 mutations	Ibrutinib	NCT02219737	18+
DHL	MYC aberrations	CUDC-907	NCT02674750	18+
PMLBCL	Programmed death-1	Pembrolizumab	NCT02576990	18+
	NF-κB activation			
	CD30	Brentuximab vedotin	NCT02423291	18+
	JAK2 mutations	Ruxolitinib	NCT01965119	19-80
	REL amplifications			
ALCL				
ALK^+	CD30	Brentuximab vedotin	NCT01777152	18+
	ALK fusion protein	Crizotinib	NCT01979536	0-21
ALK^-	CD30	Brentuximab vedotin	NCT01777152	18+

DLBCL and BL), which featured a rituximab randomization for those with high-risk disease (stage III with LDH > 2X ULN, stage IV, and Burkitt leukemia; NCT01516580). The first interim analysis indicated a survival advantage for those receiving rituximab, so the randomization was stopped.[35] The BFM reported preliminary results on a trial that incorporated a rituximab window into a BFM backbone designed for children with high-grade mature B-cell NHL (BL and DLBCL); the outcome results for this trial are pending (all patients <19 years of age).[36]

The optimal treatment of the PMLBCL subtype, which is associated with a poorer outcome than other DLBCLs in children, has yet to be defined. In the LMB-96 trial, which featured a BL-like approach, the 5-year EFS for the stage III PMLBCL was 66% (age range, 12.5-19.7 years; median, 15.7 years)—a result that was significantly less than other stage III DLBCLs treated on the same regimen (5-year EFS, 85%; $P < .001$).[37] In contrast to what has been observed in children, adults with PMLBCL have a better prognosis than adults with other DLBCL subtypes.[19] The highly successful DA-EPOCH-R regimen used in adults with PMLBCL[38] (ages 19-52 years; median, 30 years) is currently being studied in children in an international trial (NCT01516580).

Adult. The most significant improvements in outcomes for adults with DLBCL has been achieved with the addition of rituximab (R) to CHOP as reported by Coiffier, in older adults.[39] The MinT trial demonstrated an improvement in progression-free survival (PFS) (6-year 80% vs 64%) and overall survival (OS) (6-year 90% vs 80%) with the addition of rituximab to 6 cycles of CHOP in younger adults 18 to 60 years old with stage II-IV disease.[40] The RICOVER-60 trial confirmed Coiffier's results in patients aged 61 to 80 years and demonstrated that 6 cycles were equivalent to 8 cycles.[41] The LNH03-6B study further defined that every 3-week therapy was equivalent to dose-dense therapy in the era of rituximab.[42] The addition of rituximab to CHOP induction therapy has also largely obviated the need for autologous stem cell transplant consolidation for patients in CR1.[43] Finally, the attenuated immunochemotherapy regimen *R*-mini-CHOP suggests that the benefits of rituximab can be extended to the elderly and frail.[44]

Adults with DHL are often treated with DA-EPOCH-R, with consideration of autologous stem cell consolidation in CR1,[45] though this approach has not been validated in prospective studies.

Outcomes for adults with PMBLC using DA-EPOCH-R without radiation are outstanding[38]—other regimens have also been shown to be active in PMBLC.[46]

In contrast to the pediatric regimens, *R*-CHOP-21 does not routinely include central nervous system (CNS) prophylaxis. CNS prophylaxis is reserved for adults with increased risk for CNS disease (NCCN guidelines). The optimal CNS prophylaxis regimen remains controversial, but recent data favor systemic high-dose methotrexate over intrathecal therapy.[47-49]

How does the field move beyond *R*-CHOP-21? DA-EPOCH-R is currently being compared with *R*-CHOP in DLBCL based on phase 2 studies (CALGB 50303),[50-52] but its use off-study currently remains a category 2B recommendation by the NCCN. Several new agents are also being tested and may help to improve patient outcomes. These include the novel anti-CD20 obinutuzumab and the BCL-2 inhibitor venetoclax with CHOP (NCT02055820), lenalidomide in combination with DA-EPOCH-R or *R*-CHOP (NCT02213913, NCT00670358), ibrutinib with obinutuzumab, and CHOP (NCT02670317) and brentuximab vedotin with *R*-CHOP.

AYA Recommendations. Most AYA patients ages 16 to 21 years with DLBCL referred to a children's hospital, will be treated with a BL-based regimen (± rituximab). Regimens featuring rituximab, such as *R*-CHOP and DA-EPOCH-R, have excellent results in an older population with no direct comparisons of the adult *R*-CHOP/DA-EPOCH-R with pediatric Burkitt–based approaches in the AYA population. Considerations for older AYA patients (21-39 years) who do not chose to participate in a clinical trial include risk adapted adult regimens discussed before.

Burkitt lymphoma

Biology. Burkitt lymphoma is a mature B-cell lymphoma expressing surface immunoglobulin (sIg) and a spectrum of surface B-cell markers (CD19, CD20, CD22): CD10, BCL6, CD38, CD77, and CD43.[15] These lymphomas are also characterized by the presence of a reciprocal translocation involving the *c-myc* gene and one of the immunoglobulin genes. The t(8;14) is considered the classical translocation and involves the heavy-chain Ig gene on chromosome 14, and the t(8;22) and t(2;8) translocations are considered the variant translocations involving the light-chain immunoglobulin genes. Other genetic changes that have been observed in BL include 13q gains or losses, 11q gains or losses, and mutations in *ID3* and/or *TCF3*.[20] Gains and losses in 13q have been associated with a poorer prognosis. Gains or losses in 11q have been associated with *MYC* negative BL. *ID3* and or *TCF3* mutations have been associated with sporadic BL but not DLBCL.[20]

A study of cytogenetic abnormalities in adults and pediatric patients found no age-associated difference within the spectrum of cytogenetic abnormalities; however, there were age-related differences with respect to prognosis. In this cytogenetic study, abnormalities in chromosome 22q and 13q appeared to be associated with adverse risk in the pediatric population, whereas abnormalities in chromosome 17 was associated with adverse risk in adults.[53] Gene expression profiling and comparative genomic hybridization profiling have not shown significant differences between adult and pediatric BL.[20]

Gene profiling studies of BL demonstrate molecular features that distinguish it from the DLBCLs.[54] In the study by Dave et al, those patients with morphologic DLBCL with an expression profile more consistent with BL (mBL) had a poorer outcome when treated with CHOP as compared with those treated with more aggressive regimens.[20,54]

Treatment

Pediatric. The CCG trial comparing the alkylator-based COMP regimen with the multiagent acute lymphoblastic leukemia (ALL)-like regimen demonstrated a superior outcome for children with BL treated with the COMP regimen.[55] Since that time, further improvements have been achieved by intensification of therapy including the addition of HDMTX (high-dose methotrexate), cytarabine, etoposide, and aggressive CNS prophylaxis/treatment. One of the most widely used regimens was the LMB-89 regimen, which featured 3 arms (Groups A, B, and C) of therapy based on risk.[30] The current criteria for these group designations are as follows: Group A comprises those with completely resected limited-stage disease, Group C includes those with CNS involvement and/or ≥25% lymphoma blasts in the bone marrow, and Group B includes those not meeting the criteria for either Group A or C. Outcomes with this regimen were excellent. A subsequent international trial demonstrated that reductions could safely be made in the Group B arm (age range, 2.5-20.5 years) but resulted in worse outcome in the Group C arm (all patients <20 years of age).[29,31] The BFM designed a study featuring a rituximab window and BFM backbone designed for children with BL and DLBCL; the outcome results for this trial are pending.[36] A current international COG/SFOP (French Society of Pediatric Oncology) trial for children with BL and DLBCL demonstrated a survival advantage for those higher-risk (stage III with LDH > 2X ULN, stage IV and Burkitt leukemia) patients (all <18 years of age) who were randomly selected to receive rituximab (NCT01516580).[35]

Adult. The approaches for treating adults with BL largely mirror the approaches implemented in pediatrics, with excellent results for most patients.[56-58] Examples include the CODOX/IVAC regimen[57] *R*-Hyper-CVAD regimen,[52,56] and DA-EPOCH-R.[59] The very successful pediatric LMB-based approach has also been shown to be very active in adults.[58] In this regard, Soussain et al reported a 3-year OS rate in a retrospective analysis of 65 adults (17-65 years of age; median, 26 years; mean, 30 years) with BL/Burkitt leukemia treated with LMB pediatric protocols.[58] All regimens include a dose-intense schema and intrathecal therapy.

AYA recommendations. There is little controversy regarding the optimal approach to treating patients with BL in the AYA group because the regimens used in both children and adults are quite similar. The therapeutic options for AYA with BL include currently open clinical trials or the aforementioned published regimens, with a consideration for the addition of rituximab in some cases. In this regard, higher-risk patients (stage III with LDH > 2X ULN, stage IV, and Burkitt leukemia) have been shown to benefit from the addition of rituximab (NCT01516580)[35]. Although DA-EPOCH-R has been quite active in adults with BL, it is unclear whether this approach would be successful in cases of CNS+Burkitt leukemia.

Anaplastic large-cell lymphoma

Biology. Anaplastic large-cell lymphoma (ALCL) was first described by Stein as a pleomorphic large-cell lymphoma with anaplastic morphology and expressing CD30.[15,60] The ALCLs are primarily of T-cell immunophenotype, although null-type and B-lineage cases have rarely been reported. The t(2;5) translocation is commonly associated with this lymphoma and features a fusion gene comprising *NPM* and *ALK*[61]; however, variant translocations involving ALK and another partner gene may occur in some cases. The protein product can be detected with immunohistochemistry stains for ALK in both cytoplasm and nucleus for cases containing the t(2;5) and in the cytoplasm alone in cases with the variant *ALK* translocations. Effectors downstream of *ALK*, including *RAS/ERK*, *PI3K/AKT*, and *JAK3/STAT3* pathways, may be potential therapeutic targets.[20]

The frequency of genetic abnormalities varies with age in ALCL. Most pediatric cases of ALCL are *ALK*-positive. Among adults, *ALK*-positive patients are typically younger (median age 28-34 years, range 6-77 years) than *ALK*-negative patients (median age 58 years, range 22-94 years).[16,62] Emerging prognostic markers such as *DUSP22* (median age 54 years, range 36-76 years) and TP63 (median age 48 years, range 30-73 years) are largely restricted to adult populations and are rarely seen in pediatric patients. Regarding impact on prognosis, the 30% of *ALK*- negative patients that had *DUSP22* rearrangements had a 5-year OS of 90%, in contrast to the 8% of *ALK*-negative patients with TP63 rearrangements who had a 5-year OS of 17%. "Triple-negative" ALCL patients had an intermediate prognosis with a 5-year OS of 42%.[16] Studies have suggested that *ALK*-negative *DUSP22*-positive ALCL may be morphologically distinct from other *ALK*-negative ALCL.[63]

The prognosis for children with ALCL is superior to that observed in adults, which may be driven by the differences in biology described here before. Among adults, the outcome for those with *ALK*- positive ALCL is superior to that for those with *ALK*-negative disease.[17,64] In fact, the outcome for adults with *ALK*-positive ALCL approaches that described for children with ALCL (usually *ALK*-positive), suggesting that biology is a key prognostic factor independent of age in ALCL.

Treatment

Pediatric. Varied approaches have been used in the management of pediatric ALCL and range from CHOP-based approaches to those designed for the treatment of BL, with fairly comparable treatment results. The 2 most recently used regimens are the anthracycline-based APO regimen[65] (doxorubicin, vincristine, prednisone) given every 21 days for approximately 1 year, and the BFM Burkitt-like backbone approach used in the ALCL99 European trial (age range, 4 months to 19.5 years; median, 11 years).[66] The ALCL99 approach has a total cumulative anthracyline dosage less than that in the APO regimen; however, it is more intensive with increased risk for fever and neutropenia. A 3-year EFS of ~70% was achieved with both regimens. Encouraging results from the study of single-agent vinblastine[67] in patients with relapsed ALCL prompted its inclusion in 2 multicenter randomized trials in an effort to improve outcome. The ALCL99 trial randomized the use of vinblastine in higher-risk patients in the context of a previously reported and successful BFM Burkitt-like backbone (eligibility, age <22 years).[68] Concurrently, the COG randomized the use of vinblastine for advanced-stage patient in the context of an APO backbone (age range 0.7-20 years).[69] Both studies failed to show an improvement in outcome, with the addition of vinblastine into the backbone regimens.[68,69]

Factors associated with adverse risk include ALK antibody status, minimal disseminated disease (MDD), and minimal residual disease (MRD), and may be used to risk stratify-therapy.[20,70]

Targeted therapeutic approaches have been shown to be active in adults and children with relapsed ALCL. The antibody drug conjugate, brentuximab vedotin, which targets CD30, has demonstrated safety and activity in phase 1 and 2 trials.[71,72] Crizotinib, a small-molecule inhibitor of *ALK*, has also been shown to be active and well tolerated in both children and adults.[73] In this regard, both brentuximab vedotin and crizotinib have both been incorporated into the current frontline COG trial for children with newly diagnosed ALCL (NCT01979536).

Adult. Current adult NCCN guidelines recommend multiagent anthracycline-based regimens for ALCL (NCCN version 2.2016). NHL-B1 suggests that CHOEP is superior to CHOP (either every 2 or 3 weeks) in patients aged 18 to 60 years with normal LDH with aggressive lymphomas, with an improvement in 5-year EFS from 55% to 61% (every 2 weeks vs every 3 weeks) to 69% ($P = .004$).[12] NHL-B2 suggests that CHOP-14 is superior to CHOP-21 (5-year EFS 33% vs 44%, $P = .003$) in patients with aggressive lymphomas aged 61 to 75 years and that the addition of etoposide is too toxic in older patients.[13] Though ALCL patients represented a minority of patients on these studies (9.4% and 3.5%, respectively), these studies examined the role of etoposide and dose intensification in the prerituximab era across aggressive lymphomas and provide the foundation for the NCCN recommendations in ALCL. NHL B-1 and B-2 only included routine CNS prophylaxis for patients with lymphoblastic disease.

Adults with *ALK*-positive disease are believed to have better outcomes than those with *ALK*-negative disease when treated with CHOP-like regimens (5-year PFS 70% in ALK^+ vs 49% in ALK^- disease).[16,62] DA-EPOCH may be a promising approach to both ALK+ and ALK$^-$ disease, with a reported 5-year PFS of 80% and 71%, respectively, though reported numbers were small and *DUSP22* and *TP63* status were unknown and unbalances may have influenced outcomes (age range 19-68 years, median 38 years).[74]

The French reported favorable outcomes with consolidative autologous stem cell transplant in CR1 in patients with ALCL, though 7 of 15 patients were ALK^+.[75] The Nordic NLG-T-01 trial suggested that consolidative autologous stem cell transplant in CR1 may be beneficial for patients with ALK^- disease, but again numbers were small (31 patients) and biological subtypes were unknown.[76] Others have reported similar results in single-arm studies, suggesting a benefit for autologous stem cell transplant in CR1.[77-80] In contrast, a Cochrane review suggested that consolidative autologous stem cell transplant in CR1 did not benefit patients with aggressive NHL but further, ideally randomized, studies are needed to clarify this point.[81] Future studies will need to stratify patients with emerging prognostic variables such as *DUSP22* and *TP63*.

Fueled by encouraging results in advanced disease, brentuximab vedotin and crizotinib are being studied in frontline trials in ALCL.[82] As a single agent, brentuximab vedotin produced an 86% objective response rate (ORR) among 58 patients with relapsed or refractory ALCL enrolled in the study (number of patients treated by *ALK* status: ALK^-, n = 42 (72%) and ALK^+, n = 16 [28%]), with a median duration of response of >1 year.[72] Similarly, crizotinib has produced ORR of 90% in patients with relapsed or refractory ALK^+ ALCL with a 2-year PFS of 64%.[83,84] Ongoing studies in adult ALCL include the substitution of brentuximab vedotin for vincristine on the CHOP backbone as firstline therapy in CD30$^+$ mature T-cell lymphomas (ECHELON-2) (NCT01777152).

AYA recommendations. There are no data suggesting a clear advantage for any single regimen in the treatment of ALCL, regardless of age. Nevertheless, the risks and benefits of different regimens should be considered. Therapeutic options for AYA patients with newly diagnosed ALCL include open clinical trials featuring novel targeting agents. Alternatively, other aforementioned regimens can be considered.

Lymphoblastic lymphoma

Biology. Lymphoblastic lymphomas (LLs) comprise both precursor-T and precursor-B phenotypes.[15] Among the pediatric age group, the majority have a precursor-T immunophenotype. They are characterized by the expression of various surface markers as detected by immunohistochemistry or flow cytometry. The cytogenetic features of T-lymphoblastic lymphoma are less well described than other NHL subtypes in children. Chromosomal abnormalities have been described in T-ALL and T-LL which involve the *TCR* genes and result in the juxtaposition of an oncogene with the regulatory regions of the TCR genes. Examples of oncogenes involved in these translocations in T-LL include *TAL1*, *LMO2*, *LYL1*, *HOXA9*, *TLX1*, and *TLX3*.[20] Among children with T-LL, Notch 1 mutations have been associated with a better prognosis, whereas LOH6q (loss of heterozygosity at 6q) is associated with a poorer prognosis.[85] A poorer prognosis has also been associated with absence of biallelic *TRG* deletion (ABD) and *PTEN* mutations.[20]

Although T-ALL and T-LL share some of the same cytogenetic and molecular abnormalities, genomic studies featuring RNA-expression profiling and whole-exome sequencing analysis have suggested some differences between T-ALL and T-LL.[20,86] Additional next-generation sequencing studies are clearly needed to more comprehensively compare these entities. There are very limited data on the biology of B-LL. Molecular characterization of these tumors is needed both for clarifying the pathogenic mechanisms compared with B-ALL and, more importantly, to identify molecular lesions for which novel targeting agents can be used as has been done in B-ALL.

Treatment

Pediatric. Current strategies for the treatment of LL have largely been derived from successful approaches to the treatment of T-ALL.[87-91] These regimens generally comprise induction (vincristine, daunorubicin, asparaginase, and a corticosteroid), consolidation, continuation, and re-induction/reintensification phases. With contemporary treatment protocols, a 5-year EFS of 80% to 85% can be achieved for children with advanced-stage LL. Several trials have demonstrated that prophylactic cranial irradiation can be safely eliminated without compromising outcome.[88-90] Two randomized trials in the United States demonstrated that HDMTX can be safely eliminated for most children with LL, as long as sufficient intrathecal chemotherapy is administered.[90,92]

There are no clinical features that have been shown to have reliable prognostic significance. The measurement of minimal disseminated disease (MDD) in the bone marrow at diagnosis has been shown to have prognostic significance.[93] Current trials are including this risk factor in trial design with some form of intensification for those with increased MDD. Some children with B-LL have been treated on the same protocol/regimen as that used for T-LL (eg, COG A5971),[90] and not modified based on biological features as is done with B-ALL—the consequence of limited biological data for B-LL. Other current protocols are phenotype-specific and therefore include patients with T-LL and T-ALL on the same protocol, which is distinct from the protocol designed to include both B-LL and B-ALL.

Adult. The GMALL studies for adults with LL mirror to some degree the ALL-like approach used in children, featuring induction, consolidation, and re-intensification phases, delivered over 6 to 12 months.[94] In contrast, most contemporary pediatric regimens are given over 2 to 2.5 years. MD Anderson Cancer Center also implemented the hyper-CVAD regimen for adults with LL, and reported estimated 3-year PFS and OS rates of 66% and 70%, respectively (age range 17-59 years, median 28 years).[95] Other trials for adults with LL have incorporated an intensification phase with hematopoietic stem cell transplant support,[96] an approach that is not used in pediatric regimens. The treatment outcome for adults is inferior to that achieved in children.[4] The reasons for this are not entirely clear and may be secondary to as yet unidentified biological differences in lymphoma pathology or differences in tolerance of intensive ALL-based therapy. Adults with B-LL are often treated with regimens used for B-ALL and may incorporate novel agents.

AYA recommendations. There are no clear data indicating that one treatment approach is superior to others. Among patients who are not eligible for or who do not chose to enroll in a contemporary clinical trial, previously published approaches as listed before can be considered. The risk and benefits of previously published approaches will help determine the optimal approach individual AYA patients.

Follicular lymphoma

Biology. The follicular lymphomas (FLs) are mature low-grade B-cell neoplasms characterized by expression of sIg, CD10, CD20, CD22, CD23, CD79a, BCL-6. and BCL-2; the t(14;18) translocation is present in some cases.[15] More recently, "pediatric subtype" has been recognized in the World Health Organization classification.[97] Although this is a clonal B-cell process as indicated by IgR, the tumors are typically BCL-2$^-$ on immunohistochemistry stain and lack the t(14;18). This pediatric subtype is generally associated with limited stage and excellent outcome with conservative approaches. Although most children with FL have the "pediatric" subtype, some present with advanced-stage disease and are found to have the classical adult type. Conversely, some adults have been found to have the pediatric subtype and have excellent outcomes as observed in children.[98]

Treatment

Pediatric. Historically, most children with FL have received some type of conservative management approach, which generally includes surgical resection and chemotherapy, although some have been treated successfully with surgery alone.[99,100] In this regard, most children with completely resected "pediatric" FL (BCL-2$^-$ and lacking the t(14;18)) are currently treated with close observation without chemotherapy or radiotherapy. Additional data for this "watchful waiting" approach are needed.[100]

Adult. The approaches to treating adults with FL are quite varied and include complete resection, low-dose chemotherapy, immunotherapy including rituximab, intensification strategies such as hematopoietic stem cell transplant, and other modalities such as involved field radiation therapy. These approaches have been reviewed in detail.[101] Of note, adults with the "pediatric type" of FL do well with conservative management, as is the case in children.[98]

AYA recommendations. The most important determinant to treatment approach is whether the patient has the "pediatric" subtype of FL. If they do, conservative approaches with complete surgical resection of limited-stage disease and watchful waiting are reasonable. If the pathology indicates a nonpediatric FL, any of the adult approaches can be considered depending on presenting risk factors.

Conclusions

There is clearly a need for trials that span the complete age range of the pediatric and AYA groups (ie, ages 1-39 years). This will permit more accurate age-related comparisons regarding outcome and toxicity. Moreover, these trials should incorporate sophisticated molecular studies (eg, next-generation sequencing) of the lymphoma biopsy samples. This will be particularly important for the DLBCL and ALCL histologic subtypes, where striking age-associated biological differences have already been discovered that have both prognostic and therapeutic design implications. Another important challenge is the refinement of a multidisciplinary approach to diagnosis. Currently, most clinicians attempt to make the diagnosis of NHL with the least invasive approach such as interventional radiological–directed fine-needle biopsy; however, this strategy often does not provide enough tissue for more comprehensive biological characterization of the tumors. This challenge must be addressed in the context of a research trial and may necessitate re-biopsy.

The use of Web sites that review the availability of open clinical trials for AYA patients with NHL should provide AYA patients with better access to novel treatment approaches. It has been suggested that trained

navigators would be important advocates for some AYA patients seeking help in reviewing Web site options and in dealing with barriers to contemporary therapy.[3] The rapidly increasing knowledge of the complex molecular pathology of NHL in the pediatric and AYA populations, coupled with the rapidly expanding armamentarium of novel biological and targeting agents, will require some degree of subspecialization within the pediatric and adult medical oncology communities.

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Correspondence

John T. Sandlund, St. Jude Children's Research Hospital, 262 Danny Thomas Pl, Memphis, TN 38105; e-mail: john.sandlund@stjude.org.

References

1. Sandlund JT, Downing JR, Crist WM. Non-Hodgkin's lymphoma in childhood. *N Engl J Med*. 1996;334(19):1238-1248.
2. Minard-Colin V, Brugières L, Reiter A, et al. Non-Hodgkin Lymphoma in Children and Adolescents: Progress Through Effective Collaboration, Current Knowledge, and Challenges Ahead. *J Clin Oncol*. 2015; 33(27):2963-2974.
3. Wood WA, Lee SJ. Malignant hematologic diseases in adolescents and young adults. *Blood*. 2011;117(22):5803-5815.
4. Jaglowski SM, Linden E, Termuhlen AM, Flynn JM. Lymphoma in adolescents and young adults. *Semin Oncol*. 2009;36(5):381-418.
5. Sandlund JT. Should Adolescents with NHL Be Treated as Old Children or Young Adults? *Hematology Am Soc Hematol Educ Program*. 2007; 2007:297-303.
6. Bleyer A. Young adult oncology: the patients and their survival challenges. *CA Cancer J Clin*. 2007;57(4):242-255.
7. Burkhardt B, Zimmermann M, Oschlies I, et al; BFM Group. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. *Br J Haematol*. 2005;131(1):39-49.
8. Sandlund JT. Non-Hodgkin Lymphoma in Children. *Curr Hematol Malig Rep*. 2015;10(3):237-243.
9. Fintel AE, Jamy O, Martin MG. Influence of insurance and marital status on outcomes of adolescents and young adults with acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk*. 2015;15(6):364-367.
10. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med*. 1993;329(14):987-994.
11. Crom WR. Pharmacokinetics in the child. *Environ Health Perspect*. 1994;102(suppl 11):111-117.
12. Pfreundschuh M, Trümper L, Kloess M, et al; German High-Grade Non-Hodgkin's Lymphoma Study Group. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. *Blood*. 2004;104(3):626-633.
13. Pfreundschuh M, Trümper L, Kloess M, et al; German High-Grade Non-Hodgkin's Lymphoma Study Group. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. *Blood*. 2004;104(3):634-641.
14. Relling MV, Pui CH, Sandlund JT, et al. Adverse effect of anticonvulsants on efficacy of chemotherapy for acute lymphoblastic leukaemia. *Lancet*. 2000;356(9226):285-290.
15. Swerdlow SH CE, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. *IARC Press*. 2008.
16. Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. *Blood*. 2014;124(9):1473-1480.
17. Vose J, Armitage J, Weisenburger D; International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol*. 2008;26(25):4124-4130.
18. Perkins SL. Are pediatric and adult diffuse large B-cell lymphoma the same disease? *Pediatr Blood Cancer*. 2006;46(7):847.
19. Roschewski M, Dunleavy K, Wilson WH. Moving beyond rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone for diffuse large B-cell lymphoma. *Leuk Lymphoma*. 2014;55(11):2428-2437.
20. Miles RR, Shah RK, Frazer JK. Molecular genetics of childhood, adolescent and young adult non-Hodgkin lymphoma. *Br J Haematol*. 2016;173(4):582-596.
21. Miles RR, Raphael M, McCarthy K, et al; SFOP/LMB96/CCG5961/ UKCCSG/NHL 9600 Study Group. Pediatric diffuse large B-cell lymphoma demonstrates a high proliferation index, frequent c-Myc protein expression, and a high incidence of germinal center subtype: Report of the French-American-British (FAB) international study group. *Pediatr Blood Cancer*. 2008;51(3):369-374.
22. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004;103(1):275-282.
23. Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. *Blood*. 2015;125(1):22-32.
24. Thunberg U, Amini RM, Linderoth J, Roos G, Enblad G, Berglund M. BCL2 expression in de novo diffuse large B-cell lymphoma partly reflects normal differences in age distribution. *Br J Haematol*. 2009; 146(6):683-684.
25. Oschlies I, Klapper W, Zimmermann M, et al. Diffuse large B-cell lymphoma in pediatric patients belongs predominantly to the germinal-center type B-cell lymphomas: a clinicopathologic analysis of cases included in the German BFM (Berlin-Frankfurt-Munster) Multicenter Trial. *Blood*. 2006;107(10):4047-4052.
26. Salaverria I, Philipp C, Oschlies I, et al; Molecular Mechanisms in Malignant Lymphomas Network Project of the Deutsche Krebshilfe; German High-Grade Lymphoma Study Group; Berlin-Frankfurt-Münster-NHL trial group. Translocations activating IRF4 identify a subtype of germinal center-derived B-cell lymphoma affecting predominantly children and young adults. *Blood*. 2011;118(1):139-147.
27. Oschlies I, Salaverria I, Mahn F, et al. Pediatric follicular lymphoma–a clinico-pathological study of a population-based series of patients treated within the Non-Hodgkin's Lymphoma–Berlin-Frankfurt-Munster (NHL-BFM) multicenter trials. *Haematologica*. 2010;95(2):253-259.
28. Aukema SM, Siebert R, Schuuring E, et al. Double-hit B-cell lymphomas. *Blood*. 2011;117(8):2319-2331.
29. Cairo MS, Gerrard M, Sposto R, et al; FAB LMB96 International Study Committee. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. *Blood*. 2007;109(7): 2736-2743.
30. Patte C, Auperin A, Michon J, et al; Société Française d'Oncologie Pédiatrique. The Société Française d'Oncologie Pédiatrique LMB89 protocol: highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. *Blood*. 2001;97(11):3370-3379.
31. Patte C, Auperin A, Gerrard M, et al; FAB/LMB96 International Study Committee. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. *Blood*. 2007;109(7):2773-2780.
32. Woessmann W, Seidemann K, Mann G, et al; BFM Group. The impact of the methotrexate administration schedule and dose in the treatment of children and adolescents with B-cell neoplasms: a report of the BFM Group Study NHL-BFM95. *Blood*. 2005;105(3):948-958.
33. Goldman S, Smith L, Anderson JR, et al. Rituximab and FAB/LMB 96 chemotherapy in children with Stage III/IV B-cell non-Hodgkin lymphoma: a Children's Oncology Group report. *Leukemia*. 2013;27(5): 1174-1177.

34. Goldman S, Smith L, Galardy P, et al. Rituximab with chemotherapy in children and adolescents with central nervous system and/or bone marrow-positive Burkitt lymphoma/leukaemia: a Children's Oncology Group Report. *Br J Haematol*. 2014;167(3):394-401.
35. Minard-Colin V, Auperin A, Pillon M, et al. Results of the randomized intergroup trial Inter-B-NHL Ritux 2010 for children and adolescents iwth high-risk B-cell non-Hodgkin lymphoma (B-NHL) and mature acute leukemia (B-AL): Evaluation of rituximab (R) efficacy in addition to standard LMB chemotherapy (CT) regimen [abstract]. *J Clin Oncol*. 2016;34(suppl). Abstract 10507.
36. Meinhardt A, Burkhardt B, Zimmermann M, et al; Berlin-Frankfurt-Münster group. Phase II window study on rituximab in newly diagnosed pediatric mature B-cell non-Hodgkin's lymphoma and Burkitt leukemia. *J Clin Oncol*. 2010;28(19):3115-3121.
37. Gerrard M, Waxman IM, Sposto R, et al; French-American-British/Lymphome Malins de Burkitt 96 (FAB/LMB 96) International Study Committee. Outcome and pathologic classification of children and adolescents with mediastinal large B-cell lymphoma treated with FAB/LMB96 mature B-NHL therapy. *Blood*. 2013;121(2):278-285.
38. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *N Engl J Med*. 2013;368(15):1408-1416.
39. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346(4):235-242.
40. Pfreundschuh M, Trümper L, Osterborg A, et al; MabThera International Trial Group. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2006;7(5):379-391.
41. Pfreundschuh M, Schubert J, Ziepert M, et al; German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol*. 2008;9(2):105-116.
42. Delarue R, Tilly H, Mounier N, et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. *Lancet Oncol*. 2013;14(6):525-533.
43. Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 2013;369(18):1681-1690.
44. Peyrade F, Jardin F, Thieblemont C, et al; Groupe d'Etude des Lymphomes de l'Adulte (GELA) investigators. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2011;12(5):460-468.
45. Petrich AM, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. *Blood*. 2014;124(15):2354-2361.
46. Cashen AF, Christian BA, Bartlett NL. Therapy in primary mediastinal B-cell lymphoma. *N Engl J Med*. 2013;369(3):282-283.
47. Abramson JS, Hellmann M, Barnes JA, et al. Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. *Cancer*. 2010;116(18):4283-4290.
48. Cheah CY, Herbert KE, O'Rourke K, et al. A multicentre retrospective comparison of central nervous system prophylaxis strategies among patients with high-risk diffuse large B-cell lymphoma. *Br J Cancer*. 2014;111(6):1072-1079.
49. Murawski N, Held G, Ziepert M, et al. The role of radiotherapy and intrathecal CNS prophylaxis in extralymphatic craniofacial aggressive B-cell lymphomas. *Blood*. 2014;124(5):720-728.
50. Purroy N, Bergua J, Gallur L, et al. Long-term follow-up of dose-adjusted EPOCH plus rituximab (DA-EPOCH-R) in untreated patients with poor prognosis large B-cell lymphoma. A phase II study conducted by the Spanish PETHEMA Group. *Br J Haematol*. 2015;169(2):188-198.
51. Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. *J Clin Oncol*. 2008;26(16):2717-2724.
52. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer*. 2006;106(7):1569-1580.
53. Onciu M, Schlette E, Zhou Y, et al. Secondary chromosomal abnormalities predict outcome in pediatric and adult high-stage Burkitt lymphoma. *Cancer*. 2006;107(5):1084-1092.
54. Dave SS, Fu K, Wright GW, et al; Lymphoma/Leukemia Molecular Profiling Project. Molecular diagnosis of Burkitt's lymphoma. *N Engl J Med*. 2006;354(23):2431-2442.
55. Anderson JR, Jenkin RD, Wilson JF, et al. Long-term follow-up of patients treated with COMP or LSA2L2 therapy for childhood non-Hodgkin's lymphoma: a report of CCG-551 from the Childrens Cancer Group. *J Clin Oncol*. 1993;11(6):1024-1032.
56. Thomas DA, Cortes J, O'Brien S, et al. Hyper-CVAD program in Burkitt's-type adult acute lymphoblastic leukemia. *J Clin Oncol*. 1999;17(8):2461-2470.
57. Magrath I, Adde M, Shad A, et al. Adults and children with small non-cleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. *J Clin Oncol*. 1996;14(3):925-934.
58. Soussain C, Patte C, Ostronoff M, et al. Small noncleaved cell lymphoma and leukemia in adults. A retrospective study of 65 adults treated with the LMB pediatric protocols. *Blood*. 1995;85(3):664-674.
59. Dunleavy K, Pittaluga S, Shovlin M, et al. Low-intensity therapy in adults with Burkitt's lymphoma. *N Engl J Med*. 2013;369(20):1915-1925.
60. Stein H. Ki-1-anaplastic large cell lymphoma: is it a discrete entity? *Leuk Lymphoma*. 1993;10(suppl):81-84.
61. Morris SW, Kirstein MN, Valentine MB, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. [published erratum appears in Science 1995 Jan 20;267(5196):316-7] *Science*. 1994;263(5151):1281-1284.
62. Foss FM, Zinzani PL, Vose JM, Gascoyne RD, Rosen ST, Tobinai K. Peripheral T-cell lymphoma. *Blood*. 2011;117(25):6756-6767.
63. King RL, Dao LN, McPhail ED, et al. Morphologic Features of ALK-negative Anaplastic Large Cell Lymphomas With DUSP22 Rearrangements. *Am J Surg Pathol*. 2016;40(1):36-43.
64. Gascoyne RD, Aoun P, Wu D, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. *Blood*. 1999;93(11):3913-3921.
65. Laver JH, Kraveka JM, Hutchison RE, et al. Advanced-stage large-cell lymphoma in children and adolescents: results of a randomized trial incorporating intermediate-dose methotrexate and high-dose cytarabine in the maintenance phase of the APO regimen: a Pediatric Oncology Group phase III trial. *J Clin Oncol*. 2005;23(3):541-547.
66. Brugières L, Le Deley MC, Rosolen A, et al. Impact of the methotrexate administration dose on the need for intrathecal treatment in children and adolescents with anaplastic large-cell lymphoma: results of a randomized trial of the EICNHL Group. *J Clin Oncol*. 2009;27(6):897-903.
67. Brugières L, Pacquement H, Le Deley MC, et al. Single-drug vinblastine as salvage treatment for refractory or relapsed anaplastic large-cell lymphoma: a report from the French Society of Pediatric Oncology. *J Clin Oncol*. 2009;27(30):5056-5061.
68. Le Deley MC, Rosolen A, Williams DM, et al. Vinblastine in children and adolescents with high-risk anaplastic large-cell lymphoma: results of the randomized ALCL99-vinblastine trial. *J Clin Oncol*. 2010;28(25):3987-3993.
69. Alexander S, Kraveka JM, Weitzman S, et al. Advanced stage anaplastic large cell lymphoma in children and adolescents: results of ANHL0131, a randomized phase III trial of APO versus a modified regimen with vinblastine: a report from the children's oncology group. *Pediatr Blood Cancer*. 2014;61(12):2236-2242.
70. Mussolin L, Damm-Welk C, Pillon M, et al. Use of minimal disseminated disease and immunity to NPM-ALK antigen to stratify ALK-positive ALCL patients with different prognosis. *Leukemia*. 2013;27(2):416-422.

71. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med*. 2010; 363(19):1812-1821.
72. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol*. 2012;30(18):2190-2196.
73. Mossé YP, Lim MS, Voss SD, et al. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. *Lancet Oncol*. 2013;14(6):472-480.
74. Dunleavy K, Pittaluga S, Shovlin M, et al. Phase II trial of dose-adjusted EPOCH in untreated systemic anaplastic large cell lymphoma. *Haematologica*. 2016;101(1):e27-e29.
75. Deconinck E, Lamy T, Foussard C, et al. Autologous stem cell transplantation for anaplastic large-cell lymphomas: results of a prospective trial. *Br J Haematol*. 2000;109(4):736-742.
76. d'Amore F, Relander T, Lauritzsen GF, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. *J Clin Oncol*. 2012;30(25):3093-3099.
77. Czyz A, Romejko-Jarosinska J, Helbig G, et al. Autologous stem cell transplantation as consolidation therapy for patients with peripheral T cell lymphoma in first remission: long-term outcome and risk factors analysis. *Ann Hematol*. 2013;92(7):925-933.
78. Beitinjaneh A, Saliba RM, Medeiros LJ, et al. Comparison of survival in patients with T cell lymphoma after autologous and allogeneic stem cell transplantation as a frontline strategy or in relapsed disease. *Biol Blood Marrow Transplant*. 2015;21(5):855-859.
79. Rodríguez J, Caballero MD, Gutiérrez A, et al. High-dose chemotherapy and autologous stem cell transplantation in peripheral T-cell lymphoma: the GEL-TAMO experience. *Ann Oncol*. 2003;14(12):1768-1775.
80. Kim MK, Kim S, Lee SS, et al. High-dose chemotherapy and autologous stem cell transplantation for peripheral T-cell lymphoma: complete response at transplant predicts survival. *Ann Hematol*. 2007;86(6):435-442.
81. Greb A, Bohlius J, Schiefer D, Schwarzer G, Schulz H, Engert A. High-dose chemotherapy with autologous stem cell transplantation in the first line treatment of aggressive non-Hodgkin lymphoma (NHL) in adults. *Cochrane Database Syst Rev*. 2008; (1):CD004024.
82. Foyil KV, Bartlett NL. Brentuximab vedotin and crizotinib in anaplastic large-cell lymphoma. *Cancer J*. 2012;18(5):450-456.
83. Gambacorti-Passerini C, Messa C, Pogliani EM. Crizotinib in anaplastic large-cell lymphoma. *N Engl J Med*. 2011;364(8):775-776.
84. Gambacorti Passerini C, Farina F, Stasia A, et al. Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. *J Natl Cancer Inst*. 2014;106(2):djt378.
85. Bonn BR, Rohde M, Zimmermann M, et al. Incidence and prognostic relevance of genetic variations in T-cell lymphoblastic lymphoma in childhood and adolescence. *Blood*. 2013;121(16):3153-3160.
86. Raetz EA, Perkins SL, Bhojwani D, et al. Gene expression profiling reveals intrinsic differences between T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma. *Pediatr Blood Cancer*. 2006;47(2):130-140.
87. Reiter A, Schrappe M, Ludwig WD, et al. Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: a BFM group report. *Blood*. 2000;95(2):416-421.
88. Burkhardt B, Woessmann W, Zimmermann M, et al. Impact of cranial radiotherapy on central nervous system prophylaxis in children and adolescents with central nervous system-negative stage III or IV lymphoblastic lymphoma. *J Clin Oncol*. 2006;24(3):491-499.
89. Sandlund JT, Pui CH, Zhou Y, et al. Effective treatment of advanced-stage childhood lymphoblastic lymphoma without prophylactic cranial irradiation: results of St Jude NHL13 study. *Leukemia*. 2009;23(6):1127-1130.
90. Termuhlen AM, Smith LM, Perkins SL, et al. Disseminated lymphoblastic lymphoma in children and adolescents: results of the COG A5971 trial: a report from the Children's Oncology Group. *Br J Haematol*. 2013;162(6):792-801.
91. Termuhlen AM, Smith LM, Perkins SL, et al. Outcome of newly diagnosed children and adolescents with localized lymphoblastic lymphoma treated on Children's Oncology Group trial A5971: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2012;59(7):1229-1233.
92. Asselin BL, Devidas M, Wang C, et al. Effectiveness of high-dose methotrexate in T-cell lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: a randomized study by the Children's Oncology Group (POG 9404). *Blood*. 2011;118(4):874-883.
93. Coustan-Smith E, Sandlund JT, Perkins SL, et al. Minimal disseminated disease in childhood T-cell lymphoblastic lymphoma: a report from the children's oncology group. *J Clin Oncol*. 2009;27(21):3533-3539.
94. Hoelzer D, Gökbuget N, Digel W, et al. Outcome of adult patients with T-lymphoblastic lymphoma treated according to protocols for acute lymphoblastic leukemia. *Blood*. 2002;99(12):4379-4385.
95. Thomas DA, O'Brien S, Cortes J, et al. Outcome with the hyper-CVAD regimens in lymphoblastic lymphoma. *Blood*. 2004;104(6):1624-1630.
96. Song KW, Barnett MJ, Gascoyne RD, et al. Primary therapy for adults with T-cell lymphoblastic lymphoma with hematopoietic stem-cell transplantation results in favorable outcomes. *Ann Oncol*. 2007;18(3):535-540.
97. Lorsbach RB, Shay-Seymore D, Moore J, et al. Clinicopathologic analysis of follicular lymphoma occurring in children. *Blood*. 2002;99(6):1959-1964.
98. Louissaint A Jr, Ackerman AM, Dias-Santagata D, et al. Pediatric-type nodal follicular lymphoma: an indolent clonal proliferation in children and adults with high proliferation index and no BCL2 rearrangement. *Blood*. 2012;120(12):2395-2404.
99. Sandlund JT, Perkins SL. Uncommon non-Hodgkin lymphomas of childhood: pathological diagnosis, clinical features and treatment approaches. *Br J Haematol*. 2015;169(5):631-646.
100. Attarbaschi A, Beishuizen A, Mann G, et al; European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL) and the international Berlin-Frankfurt-Münster (i-BFM) Study Group. Children and adolescents with follicular lymphoma have an excellent prognosis with either limited chemotherapy or with a "Watch and wait" strategy after complete resection. *Ann Hematol*. 2013;92(11):1537-1541.
101. Hiddemann W, Cheson BD. How we manage follicular lymphoma. *Leukemia*. 2014;28(7):1388-1395.