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Pediatric Lymphomas and Histiocytic Disorders of Childhood

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INTRODUCTION

Hodgkin lymphoma (HL) is diagnosed in approximately 1100 children and adolescents less than 20 years of age in the United States each year, accounting for 6% of overall childhood cancer diagnoses, and ranks as the most common malignancy among adolescents 15 to 19 years old.^{1,2} It is one of the most curable forms of childhood cancer, with estimated 5-year survival rates exceeding 98%, yet long-term overall survival declines primarily from delayed effects of therapy. This challenge has resulted in the development of various strategies aimed at identifying the optimal balance between maintaining overall survival and avoidance of long-term morbidity of therapy, often representing strategies quite different than those used for adults with HL. More recent advances in the understanding of the biology of HL are now being realized with the introduction of targeted therapies.

Histiocytic Disorders

Langerhans cell histiocytosis (LCH) occurs with similar frequency as HL. Patients with high-risk disseminated disease have approximately 90% long-term survival; patients with low-risk disease have almost 100% survival. However, current standard-of-care therapy fails to cure more than 50% of all patients, and long-term effects are frequent. Emerging biological data support reclassification of LCH and other histiocytic disorders, including Erdheim-Chester disease (ECD) and juvenile xanthogranuloma (JXG) as myeloid

neoplasias. Inclusion of patients with these diseases in cooperative pediatric cancer network trials is essential to optimize diagnostic and therapeutic strategies.

NON-HODGKIN LYMPHOMA

Histopathological Categories

Non-Hodgkin lymphoma (NHL) in children is distinct from the low-grade or intermediate-grade lymphomas seen in adults because almost all NHL that occurs in children is high grade.³ The World Health Organization (WHO) has classified NHL on the basis of phenotype (B vs T vs NK cell lineage) and differentiation (ie, precursor vs mature).⁴ Based on disease response to therapy, NHL in pediatric and young adult age groups falls into the following categories:

1. Mature B-cell NHL (predominantly Burkitt lymphoma [BL] and diffuse large B-cell lymphoma [DLBCL]).
2. Lymphoblastic lymphoma (LBL), which is predominantly a precursor T-cell lymphoma with precursor B-cell lymphoma being a rarer entity.
3. Anaplastic large cell lymphoma (ALCL; mature T-cell or null-cell lymphomas).
4. Posttransplant lymphoproliferative diseases (PTLD) usually have a mature B-cell phenotype including DLBCL and BL, although 10% will be mature (peripheral) T-cell lymphomas. Furthermore, PTLD is classified according to WHO nomenclature as (1) early lesions, (2) polymorphic, and (3) monomorphic.⁵

Current therapies for LBL are now based on acute lymphoblastic leukemia protocols and, therefore, the focus of the NHL section of this article is on mature B-cell NHL, ALCL, and PTLD (Table 1).

B-cell non-Hodgkin lymphoma—Burkitt lymphoma and diffuse large B-cell lymphoma—BL accounts for about 30% of childhood NHL in the United States and is generally a highly aggressive tumor.³ It is higher among boys than girls (approximately 4:1).⁶ The most common primary sites of disease are the lymph nodes (especially head and neck) and abdomen, although the disease can present at other sites including bone, skin, bone marrow, testes, and the central nervous system (CNS).⁶ The malignant cells show a mature B-cell phenotype and are terminal deoxynucleotidyl transferase-negative. The lymphoma cells usually express surface immunoglobulin with either κ or λ light chains. Additional B-cell markers such as CD20 and CD22 are usually present, and almost all express CALLA (CD10). BL expresses the characteristic chromosomal translocation juxtaposing the *c-myc* oncogene and immunoglobulin locus regulatory elements such as t(8;14) and more rarely t(8;22) or t(2;8).³ Cytogenetic evidence of *c-myc* rearrangement is the gold standard for the diagnosis of BL. The distinction between BL and Burkitt-like lymphoma/leukemia is, however, controversial and, on pathology, the latter may appear more consistent with DLBCL if there is a lack of cytogenetic evidence for BL. Studies have demonstrated that most Burkitt-like or “atypical Burkitt” lymphomas have a gene expression signature similar to BL.⁷ In addition, as many as 30% of pediatric DLBCLs will have a gene signature similar to BL.^{7,8} Despite the histologic differences, BL and Burkitt-like

lymphoma/leukemia and DLBCL are clinically very aggressive and, unlike in adults, are treated with similar regimens.^{9,10}

DLBCL represents 10% to 20% of pediatric NHL and occurs more frequently in the 10- to 20-year age group than in children less than 10 years of age.^{3,11,12} The clinical presentation of pediatric DLBCL is similar to BL, although it is more often localized and less often involves the CNS or bone marrow.^{11,12} Approximately 20% of pediatric DLBCL presents as primary mediastinal B-cell lymphoma (PMBL) and is more common in older children/young adults. It is associated with distinctive chromosomal aberrations with gains in chromosome 9p and 2p (regions that involve *JAK2* and *c-rel*, respectively),¹³ with inactivation of *SOCS1* also seen. PMBL also has a distinctive gene expression profile compared with other DLBCLs, and some suggest there is a closer relationship of this disease with HL.¹⁴ Apart from PMBL, pediatric DLBCL differs biologically from the disease seen in adults because most pediatric DLBCL have a germinal center B-cell phenotype, unlike adult DLBCL, which is more frequently associated with the ABC phenotype.¹⁵

Posttransplant lymphoproliferative disease—The incidence of lymphoproliferative disease (LPD) or lymphoma is 100-fold higher in immunocompromised children than in the general population. The cause of such immune deficiencies may be a genetically inherited or an acquired defect (eg, HIV infection) or following transplantation (solid organ transplantation [SOT] or allogeneic hematopoietic stem cell transplantation [HSCT]). Epstein-Barr virus (EBV) is associated with most of these tumors, but some cases are not associated with any infectious agent. This section focuses on PTLT, the most common setting of pediatric LPD. This disease represents a spectrum of morphologically and clinically heterogeneous lymphoproliferations. EBV is highly associated with PTLT following HSCT but EBV-negative PTLT can be seen following SOT, especially LPDs that present late post-SOT.¹⁶ The WHO has classified PTLT into the following 3 subtypes⁵:

- Early lesions: early lesions show germinal center expansion, but tissue architecture remains normal.
- Polymorphic PTLT: polymorphic PTLT shows disruption of nodal architecture and necrosis with infiltrating T cells.
- Monomorphic PTLT: monomorphic PTLT shows similar histologies to those observed in NHL, with DLBCL being the most common histology, followed by BL and then rarer subtypes.

EBV PTLT may manifest as isolated hepatitis, interstitial pneumonitis, meningoencephalitis, or an infectious mononucleosis-like syndrome. The definition of PTLT is frequently limited to lymphomatous lesions (low stage or high stage), which are often extranodal (frequently in the allograft). Although less common, PTLT may present as a rapidly progressive disease with multiorgan failure that usually results in death despite therapy.¹⁶

Anaplastic large cell lymphoma—ALCL accounts for approximately 10% of childhood NHL.¹² Although the predominant immunophenotype of ALCL is mature T-cell, null-cell disease (ie, no T-cell, B-cell, or NK-cell surface antigen expression) does occur. The WHO

classification system classifies ALCL as a peripheral T-cell lymphoma.⁴ All ALCL are CD30+ and most (>90%) pediatric ALCLs have a chromosomal rearrangement involving the *ALK* gene, and their prognosis tends to be superior to adults who generally have an *ALK*-negative disease.¹⁷ Clinically, systemic ALCL has a broad range of presentations, including lymph node as well as extranodal involvement (skin, bone, and, less commonly, lung, pleura, gastrointestinal tract, and muscle). Involvement of the CNS and bone marrow is uncommon. ALCL is often associated with systemic symptoms (eg, fever, weight loss) that can wax and wane, which may delay diagnosis.

Staging for Childhood Non-Hodgkin Lymphoma

The most widely used staging scheme for childhood NHL is that of the Murphy Staging.¹⁸ However, as shown in Table 2, patients with mature B-cell NHL (BL and DLBCL) are generally treated based on features of the disease, other than stage.

Stage I: involvement of a single tumor or nodal area excluding abdomen and mediastinum

Stage II: disease limited to a single tumor with regional node involvement, 2 or more tumors or nodal areas involved on one side of the diaphragm, or a primary gastrointestinal tract tumor (completely resected) with or without regional node involvement

Stage III: tumors or involved lymph node areas occurring on both sides of the diaphragm, including any primary intrathoracic (mediastinal, pleural, or thymic) disease, extensive primary intra-abdominal disease, or any paraspinal or epidural tumors

Stage IV: tumors involving bone marrow (>5% malignant cells in otherwise normal BM or <25% malignant cells for LBL) and/or CNS, irrespective of other sites of involvement.

Apart from LBL, the definition of CNS disease in NHL is any malignant cell present in the CSF regardless of cell count.

General Treatment Considerations

Management goals—There are 2 potentially life-threatening clinical situations that are often seen in children with NHL: (1) mediastinal masses and (2) tumor lysis syndrome, most often seen in LBL and BL. These emergent situations should be anticipated in children with NHL and addressed immediately.

Mediastinal masses: Patients with large mediastinal masses are at risk of cardiac or respiratory arrest during heavy sedation or general anesthesia. Therefore, a careful physiologic and radiographic evaluation should be carried out and the least invasive procedure should be used to establish the diagnosis, including bone marrow biopsy, pleural tap, or CT-guided core needle biopsy, keeping patients out of a supine position.^{19,20}

Tumor lysis syndrome: Tumor lysis syndrome results from rapid breakdown of malignant cells, resulting in, most notably, hyperuricemia, hyperkalemia, and hyperphosphatemia. Hyperhydration and allopurinol or rasburicase (urate oxidase) are essential treatments in all patients except those with the most limited disease.^{21,22} An initial prephase consisting of low-dose cyclophosphamide and vincristine does not obviate allopurinol or rasburicase and hydration. Gastrointestinal bleeding, obstruction, and (rarely) perforation may occur. Hyperuricemia and tumor lysis syndrome, particularly when associated with ureteral obstruction, frequently result in life-threatening complications.

Role of radiographic imaging in childhood non-Hodgkin lymphoma: Radiographic imaging is essential in the staging of patients with NHL. CT scan and, more recently, MRI have been used for staging. Radionucleotide bone scans should be considered for patients wherein bone involvement is suspected. The role of functional imaging in pediatric NHL is controversial. Gallium scans have been replaced by fluorodeoxy-glucose PET scanning. The value of PET scanning for staging pediatric NHL is, however, still under investigation. Data support that PET identifies more abnormalities than CT scanning, but it is unclear whether this should be used to change therapy.²³ The use of PET to assess rapidity of response to therapy appears to have prognostic value in HL and some types of NHL observed in adult patients, but requires investigation in pediatric NHL. Caution is also required for surveillance scanning because false-positive results are common. There are also data demonstrating that PET scanning can produce false-negative results; therefore, a biopsy to prove residual or recurrent disease is required.²⁴

Pharmacologic and novel targeted strategies

Mature B-cell non-Hodgkin lymphoma (Burkitt lymphoma and diffuse large B-cell lymphoma): Patients with low-stage (stage I/II) disease have an outstanding prognosis, regardless of histology with disease-free survival of about 95% (Table 3). Patients with high-stage (stage III/IV) mature B-lineage NHL have an 80% to 95% long-term survival.^{25,26} Unlike mature B-lineage NHL seen in adults, there is no difference in outcome based on histology (BL or Burkitt-like lymphoma or DLBCL) with current therapy in pediatric trials (Table 4).^{25,26}

Rituximab is a mouse/human chimeric monoclonal antibody targeting the CD20 antigen, which is expressed by DLBCL and BL in children and has been widely used in the treatment of adult lymphomas (eg, R-CHOP and EPOCH-R).²⁷ In children, a single-agent window phase II study of rituximab performed by the Berlin-Frankfurt-Munster group showed activity in BL.²⁸ A Children's Oncology Group (COG) pilot study (COG-ANHL01P1) added rituximab to baseline chemotherapy with FAB/LMB-96 therapy in patients with stage III and stage IV B-cell NHL. ANHL01P1 found no serious toxicities associated with the addition of rituximab, although, especially in adult studies, infectious complications with fatal viral infections have been observed. Rituximab pharmacokinetics found similar drug exposures to adult studies and was detected in serum up to 6 months after last dose. The 3-year event-free survival (EFS) rate was 93% (95% confidence interval [CI]; 78%–98%) for group B and 86% (95% CI; 70%–94%) for group C patients.²⁹ The study provided the key feasibility data for the current intergroup study (COG ANHL1131), which is currently open

within European cooperative groups, and the COG, to patients with advanced stage B-cell NHL (stage III disease with LDH >2 times normal and any stage IV disease) or mature B-cell leukemia (>25% blasts in marrow), excluding patients with PMBL.

Primary mediastinal B-cell lymphoma: This entity has been associated with an inferior outcome compared with other pediatric DLBCL (see Table 4).^{10,29,30} However, a single-arm study in adults showed excellent disease-free survival using the DA-EPOCH-R regimen (dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and rituximab; usually 6 cycles) with filgrastim and no radiation therapy. The 5-year EFS was 93% and overall survival (OS) was 97%.^{31,32} At 10 years after the study, there was no evidence of cardiac toxicity; this is currently being tested in pediatric clinical trials including part of COG-ANHL1131.

Anaplastic large cell lymphoma: The optimal treatment strategy for ALCL remains to be defined, with survival ranging from 70% to 85%, regardless of treatment.^{26,33,34} For low-stage ALCL, the best results have come from using pulsed chemotherapy similar to mature B-cell NHL therapy with 3-year EFS ranging from 80% to 88% and OS greater than 95% (see Table 3). Vinblastine appears to have significant activity in relapsed ALCL³⁵ and has been incorporated as front-line treatment in 2 randomized trials: ALCL (multinational European trial) and APO (COG trial). The COG study demonstrated no benefit with the addition of vinblastine.³⁶ In ALCL99, patients receiving vinblastine maintenance for 1 year had a better 1-year EFS than those without vinblastine (91% vs 74%, respectively); however, by 2 years, the EFS decreased to 73% for both groups.³⁷ In addition, ALCL99 showed that 1 g/m² methotrexate given over a period of 24 hours was similar to 3 g/m² over a period of 3 hours without intrathecal chemotherapy, but the latter had less acute toxicity.³⁸ The excellent activity of brentuximab vedotin (Bv; tubulin-inhibitor conjugated monoclonal anti-CD30) and crizotinib (oral ALK inhibitor) in relapsed ALCL patients^{39,40} has, however, led the COG to pursue testing the efficacy and toxicity of adding these 2 targeted agents with standard chemotherapy in newly diagnosed pediatric patients with ALCL in COG-ANHL12P1.

Posttransplant lymphoproliferative diseases: These highly immunogenic tumors express a type III latency of EBV antigen expression wherein they express all latent EBV proteins and therefore are amenable to immune-based therapies. Numerous therapeutic approaches to PTLTD have been explored in children but generally there has been a paucity of multicenter studies for this disease. Withdrawal or reduction of immunosuppression is often considered because first-line therapy response depends on whether the patient can recover sufficient T-cell function to eradicate EBV-infected B cells. After SOT, modalities such as radiotherapy or surgical resection for localized PTLTD can result in complete remissions. One study evaluated the efficacy of low-dose cyclophosphamide and prednisone for pediatric patients with PTLTD after SOT. All patients had progressed despite reduction of immune suppression and received 6 cycles of chemotherapy. The 2-year EFS and OS were 67% and 73%, respectively.⁴¹ Subsequently, the COG evaluated in a phase II study (COG-ANHL0221) the addition of rituximab to this regimen of low-dose cyclophosphamide and prednisone demonstrating an EFS and OS of 71% and 83%, respectively. To build on the success of this

first cooperative group trial for PTLD, the COG now propose to administer “off-the-shelf” third-party allogeneic EBV/latent membrane protein-CTLs⁴² to determine the safety and efficacy in patients with PTLD post SOT.

HODGKIN LYMPHOMA

Histopathological Categories

In general, HL in children and adolescents is comparable to HL observed in young adults.⁴³ HL is characterized by the presence of multinucleated giant cells (Hodgkin/Reed-Sternberg cells, H/RS) or large mononuclear cell variants (lymphocytic and histiocytic cells) in a background of inflammatory cells consisting of small lymphocytes, histiocytes, neutrophils, eosinophils, plasma cells, and fibroblasts. Nearly all cases of HL arise from germinal center B cells that cannot synthesize immunoglobulin, yet these cells account for approximately 1% of the cells in the involved areas.⁴⁴ Use of fine needle aspirates for determination of diagnosis is discouraged because of the rarity of the H/RS cells and risk for missing the diagnosis. Two broad pathologic classes exist: classical (cHL) and nodular lymphocyte predominant (NLPHL).⁴⁵

Classical Hodgkin lymphoma—cHL accounts for most childhood HL in the United States and the male-to-female ratio (M:F) varies markedly by age. Children less than 5 years of age show a strong male predominance (M:F = 5.3), whereas adolescents 15 to 19 years old show a slight female predominance (M:F = 0.8). Approximately 80% of patients present with painless adenopathy, most commonly involving the supraclavicular or cervical areas. Involvement of the anterior mediastinum, often asymptomatic, is present in about 75% of adolescents and young adults, yet only 35% of young children.⁴⁶

H/RS cells nearly always express CD30, with CD15 also expressed in approximately 70%. Other B-cell antigens, such as CD45, CD19, and CD79A, are generally not expressed on the H/RS cell.⁴⁷ CD20 is expressed in approximately 6% to 10% of cHL, which is further subdivided into 4 main histologic subtypes: (1) lymphocytic: H/RS cells exist in a background predominantly of lymphocytes; (2) mixed cellularity: H/RS cells are frequent in a background of abundant normal reactive cells; (3) nodular sclerosis: most common subtype in adolescents (77%) and young adults (72%) compared with younger children (44%).⁴⁸ Collagenous bands divide the lymph node into nodules that often contain an H/RS cell variant called the lacunar cell; and (4) lymphocyte-depleted: rarely observed in children and adolescents and more commonly confused with ALCL, often presents as disseminated disease and associated with a poorer prognosis. EBV-positive cHL is frequently associated with the mixed cellularity subtype and is generally more common in male patients. EBV+ cHL is especially notable for a high incidence in developing countries.⁴⁹ EBV is identified in H-RS cells by the presence of EBV-encoded RNA in situ hybridization and/or latent membrane protein by immunohistochemistry.

Nodular lymphocyte predominant Hodgkin lymphoma—NLPHL accounts for 5% to 10% of childhood HL.⁵⁰ The characteristic lymphocyte and histiocytic cells express CD20, and rarely, CD30 and CD15. A prognostic score incorporating variant histologic patterns (diffuse and T-cell-rich) along with gender and serum albumin has been recently

reported.⁵¹ NLP HL tends to be indolent with a lengthy time to diagnosis and propensity for multiple late relapses. Although the overall prognosis is favorable, a higher risk for transformation or development of DLBCL is observed.⁵² It is more common in children less than 10 years old, wherein it commonly involves a single peripheral lymph node region and infrequently involves the mediastinum.⁵⁰ Expression of EBV is rarely reported.⁵³

The risk of both cHL and NLP HL is increased in individuals with an underlying or acquired immunodeficiency disorder, although the overall risk is not as high as that observed for NHL. However, specific defects, such as seen in those individuals with fas mutation–associated autoimmune lymphoproliferative syndrome, have a 51-fold increased risk for all types of HL and 14-fold increased risk for NHL.⁵⁴ HL associated with HIV infection is more common with moderate rather than severe immunosuppression, especially with the advent of highly active antiretroviral therapy.⁵⁵ Mixed cellularity subtype and presence of extranodal involvement are typical.

Staging for Childhood Hodgkin Lymphoma

Physical examination and diagnostic imaging evaluations (upright posteroanterior and lateral thoracic radiographs; CT of the neck, chest, abdomen, and pelvis with intravenous and oral contrast; and functional nuclear imaging studies with FDG-PET) are used to designate a clinical stage. Data from retrospective studies suggest that FDG-PET may replace the need for bone marrow biopsies in patients with clinical stage III to IV disease or B symptoms; however, this has not been prospectively validated.⁵⁶ Staging laparotomy is rarely appropriate with the imaging modalities available today, but biopsy of specific sites with equivocal findings by clinical staging should be considered when results will alter therapy.

The most widely used staging scheme for both childhood and adult HL is that of the Ann Arbor Staging,⁵⁷ a system primarily developed to facilitate delivery of radiotherapy. Following the identification of the prognostic importance of bulky disease (>10 cm in maximum dimension on CT), this factor was incorporated with the Cotswolds modification.⁵⁸ However, as shown in Table 5, treatment allocation is based on several prognostic factors, other than just stage, and varies considerably across different clinical trials consortia.

Stage I: involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)

Stage II: involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of extralymphatic organ or site and of 1 or more lymph node regions on the same side of the diaphragm (IIE)

Stage III: involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS), or both (IIISE)

Stage IV: diffuse or disseminated involvement of 1 or more extralymphatic organs or tissues (eg, bone marrow, liver, lungs) with or without associated lymph node enlargement.

Each stage is further subdivided into A and B categories, with B denoting those with constitutional symptoms, present in approximately 26% to 38% of childhood HL.^{59,60} B symptoms include (1) unexplained weight loss of more than 10% of the body weight in the 6 months before diagnosis; (2) unexplained fever with temperatures greater than 38°C; and (3) drenching night sweats. Pruritus alone is not considered a B symptom. Short, febrile illness associated with a known infection similarly does not qualify for B classification.

General Treatment Considerations

Management goals

Risk stratification: With the high cure rates observed in children and adolescents with HL, the ongoing focus has been on the development of less toxic therapy. Recent pediatric HL trials have investigated titration of therapy because of risk group stratification using clinical prognostic factors, with further refinement through assessment of interim or end of chemotherapy response in most cases. Presenting features at diagnosis, including B symptoms, mediastinal and peripheral lymph node bulk, extranodal extension of disease to contiguous structures, number of involved nodal regions, Ann Arbor stage, serum markers of inflammation, and gender, as well as response to initial chemotherapy, are used for risk stratification. Stage IV disease, fever, low serum albumin, and bulky mediastinal mass, along with early response measured by CT and to a lesser extent FDG-PET, were strong predictors of EFS in a COG study.⁴⁶ Unfortunately, there is no uniform risk stratification algorithm in pediatric HL (see Table 5).

Role of radiographic imaging in childhood Hodgkin lymphoma: Functional imaging has a larger role in the management of HL as compared with NHL. Similar to NHL, stage migration occurs; however, despite this limitation, its use is now routine.⁶¹ As is the case for HL in adults, interim assessment of response by FDG-PET is incorporated into contemporary treatment approaches; however, the optimum time point for assessment and the criteria for response have not been defined. Continued surveillance for relapse with FDG-PET in the after-treatment period is not recommended because of its low positive predictive value.⁶²

Pharmacologic and novel targeted strategies

Classical Hodgkin lymphoma: Recent trials (summarized in Tables 6–8) have used chemotherapy regimens of varying dose intensity and have significant differences in the criteria for omission of radiotherapy. The European consortium has investigated OEPA (vincristine, etoposide, prednisone, doxorubicin) for low risk, and OEPA with COPDac (cyclophosphamide, vincristine, prednisone, dacarbazine) for intermediate-risk and high-risk groups. In North America, the COG has primarily evaluated ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide) and its derivatives across the risk groups.

Radiotherapy usage varies considerably. The COG recently reported that radiotherapy may be safely omitted in intermediate-risk patients who have a rapid reduction in tumor

dimensions by CT after 2 cycles of chemotherapy.⁴⁶ The European Consortium has omitted radiotherapy for low-risk patients achieving a complete response after 2 cycles of OEPA.⁶⁰ In general, pediatric radiotherapy approaches use lower doses (15–25 Gy) and fields (involved field or node).⁶³

Bv, a murine/human chimeric monoclonal conjugate linked to monomethyl auristatin E (vedotin) that targets the CD30 antigen expressed on H/RS cells, is approved for relapsed/refractory HL, after results from a pivotal phase 2 trial in adults with relapsed HL following autologous stem cell transplant demonstrated a 34% complete response and 40% partial response with a median duration of response of 6.7 months.⁶⁴ Bv in conjunction with doxorubicin, vinblastine, and dacarbazine is safe and associated with a very high complete response rate.⁶⁵ Its efficacy is being evaluated in a large international phase 3 trial in adults (clinicaltrials.gov # NCT01777152). In COG, Bv will be incorporated into a slightly modified version of ABVE-PC, termed Bv-AVEPC, in a phase 3 trial for high-risk HL (clinicaltrials.gov # NCT02166463). Sensory peripheral neuropathy has been observed in adults receiving Bv for HL and will be carefully monitored in the upcoming trial.

The focus on balancing efficacy with long-term toxicities continues into the management of patients with relapsed HL. In contrast to NHL, the prognosis for relapsed HL is generally favorable. Although high-dose chemotherapy and autologous hematopoietic stem cell transplantation (AHSCT) are still considered the standard approach for most patients with relapsed/refractory HL, a subset of children with low-risk relapse do not require AHSCT to be cured. A proposed retrieval therapy stratification algorithm has recently been reported.⁶⁶

Nodular lymphocyte predominant Hodgkin lymphoma: Adult guidelines have included surgery only for limited disease, radiation with doses of 30 to 36 Gy, chemotherapy only, combined modality therapy, and the anti-CD20 monoclonal antibody rituximab. Given the recognition that late complications of treatment such as secondary malignancies or cardiopulmonary toxicity, or transformation to aggressive B-cell lymphoma, account for most adverse fatal events, pediatric approaches have diverged from those used in adults.⁵⁰ A recent COG trial (AHOD03P1) evaluated a reduced intensity strategy for early-stage pediatric NLPHL. Among patients with a completely resected single node, greater than 80% did not recur at 4 years. Among all other early-stage patients, 3 cycles of a low-intensity chemotherapy regimen (doxorubicin, vincristine, prednisone, and cyclophosphamide) was associated with a 4-year EFS of 88.1% with greater than 90% avoiding radiotherapy.⁴⁶

HISTIOCYTIC DISORDERS

Langerhans Cell Histiocytosis

LCH is a disease characterized by lesions that include pathologic CD207+ dendritic cells (DCs) with phenotypic similarity to epidermal Langerhans cells in a background of inflammatory cells that may include lymphocytes, eosinophils, and macrophages. Clinical manifestations of LCH range from relatively trivial single lesions to potentially life-threatening disseminated disease. Historically, the pediatric oncology community has not fully embraced LCH, likely because of the unresolved biological ambiguity of LCH as a malignancy versus inflammatory disorder. More recently, identification of recurrent somatic

mutations in *BRAF-V600E* in hematopoietic precursor cells more clearly define LCH as a true myeloid neoplasia.

Epidemiology—The incidence of LCH is approximately 5 cases per 1 million children younger than 15 years of age. There are roughly equal numbers of boys and girls affected, and the median age of presentation is 30 months, although new disease may develop throughout adulthood.^{67–70} LCH may arise concurrently in identical twins. There are occasional reports of affected nonidentical siblings, although it is not clear if this is a higher rate than would occur by chance.⁷¹ The role of inherited risk of LCH therefore remains uncertain.

Pathobiology—Until recently, research of the cause of LCH has been challenged by typical issues of rare disease research, including lack of access to viable tissue, compounded by heterogeneity of the LCH lesions and lack of reliable in vitro or animal models. For decades, LCH has been assumed to arise from neoplastic transformation or inappropriate immune activation of epidermal Langerhans cells.⁷² However, gene expression analysis of purified CD207+ cells from LCH lesions revealed a transcriptional profile more consistent with less differentiated myeloid DCs.⁷³ Next-generation sequencing strategies further revealed that DCs purified from archived biopsy specimens had high frequency of the *BRAF-V600E* somatic mutation.⁷⁴ Recurrent *BRAF-V600E* mutations have subsequently been validated in subsequent LCH cohorts.^{75–78} Interestingly, the state of differentiation in which *BRAF-V600E* mutations arise is associated with anatomic distribution of lesions and severity of disease in patients with LCH. The functional significance of acquisition of *BRAF-V600E* in specific myeloid lineages is supported by the ability to recapitulate LCH-like phenotype in mice.⁷⁸ In the authors' opinion, these data support reclassification of LCH as a myeloid neoplasia.

Clinical manifestations—LCH is a classic “morning report” disease with protean manifestations from a single skin or bone lesion to acute myeloid leukemia-like disseminated disease with multi-system organ failure. LCH lesions can involve almost any organ system: clinical “high-risk” LCH is defined by infiltration of liver, spleen, and/or bone marrow with lesions; clinical “low-risk” LCH is defined by lesions anywhere else. The most common symptoms are skin rash or painful bone lesions. Less frequent manifestations include diabetes insipidus (DI) with pituitary involvement or back pain with vertebra plana. Late effects are a significant problem for patients and may be caused by disease or therapy; progressive neurodegeneration and sclerosing cholangitis associated with LCH are particularly devastating.

Differential diagnosis—Because of the infrequent occurrence of LCH and similar appearance to candidiasis, seborrhea, eczema, and other common rashes, many infants with LCH skin lesions have symptoms for more than 1 year before diagnostic biopsy.⁷⁹ Mastoid LCH in toddlers may resemble chronic otitis media with chronic discharge. In older patients, skin lesions may resemble sexually transmitted diseases or viral infections. Lytic bone lesions require biopsy to differentiate from other primary or metastatic malignancies or infections. Patients with intestinal involvement may have symptoms and imaging also

consistent with inflammatory bowel disease. Liver, spleen, and bone marrow infiltration may resemble acute leukemia. Isolated DI may be caused by hypophysitis, germinoma, or lymphoma. Once LCH is suspected, definitive diagnosis is relatively straightforward with biopsy.

Prognosis (staging)—Patients with high-risk LCH have greater than 85% long-term survival, and patients with low-risk LCH have nearly 100% survival.⁸⁰ However, refractory or relapsed LCH is a problem for more than 50% of patients with both high-risk and low-risk multifocal disease,⁸¹ and long-term morbidity is associated with uncontrolled LCH.⁸² Although there is no standard approach to staging, a combination of imaging and laboratory tests is typically used to identify lesions and potential organ damage. In the case of infants with skin LCH, patients are often incorrectly assumed to have skin-limited disease, delaying timely diagnosis and therapy for potentially fatal occult multisystem high-risk disease.⁷⁹ In one study, PET scan was the most sensitive imaging modality for LCH. Complete evaluation is important because lesions in more than one site impact the need for systemic chemotherapy.⁸³

Therapy—Optimal therapy has not yet been completely defined with clinical trials. However, standard practice bases therapy on extent of disease. Patients with proven skin-limited disease may be observed and do not require therapy unless they are symptomatic. Single bone lesions may be cured by curettage. It is contraindicated to perform resections with surgical margins because this impairs bone remodeling, which typically occurs with resolution of LCH. Patients with multisystem disease are treated with systemic chemotherapy. The authors consider therapy based on LCHIII, the most recent Histiocyte Society trial, to be standard of care for children, which is basically 1 year of vinblastine and prednisone. In LCHIII, patients treated for 1 year had significantly fewer recurrences than patients treated for 6 months.⁸⁰ Patients with single bone lesions in sinuses, orbit, or pituitary are treated with chemotherapy because of reports of decreased risk of subsequent development of neurodegenerative disease. In an institutional study, adults with LCH had nearly universal toxicity to vinblastine and prednisone, although some were effectively treated with cytarabine chemotherapy.⁸⁴

There is no standard for treating a patient with recurrent disease, although strategies with nucleoside analogues, cladribine and cytarabine, have been effective.^{85–87} For patients refractory to other nucleoside analogues, clofarabine has been effective. In rare cases of disease refractory to any chemotherapy, stem cell transplant with reduced intensity conditioning has been curative. An early report described promising responses to vemurafanib in adults who had both ECD and LCH lesions.⁸⁸ The significant rate of toxicities associated with first-generation BRAF inhibitors makes it difficult to determine the optimal patient in whom to use these drugs, and clinical trials are ongoing in adults and children.⁸⁹

The Histiocyte Society trial LCH-IV is currently open and accruing with observational and/or therapeutic arms for patients with all manifestations of LCH (clinicaltrials.gov # NCT02205762). Additional local and cooperative clinical trial efforts are required to

identify effective novel agents and more rapidly determine optimal up-front and salvage therapy strategies for patients with LCH.

Non-Langerhans Cell Histiocytic Disorders

Juvenile xanthogranuloma—JXG has many similarities to LCH, but has a distinct pattern of presentation and histology. The precise incidence is not known, but registry data estimate it to be 5 times less common than LCH⁹⁰; there are reported associations with juvenile myelomonocytic leukemia and neurofibromatosis, diseases characterized by hyperactive Ras pathway signaling (reviewed in⁹¹).

The most common clinical manifestation is limited skin disease, as either a single lesion or multiple lesions. Less frequently, lesions may also arise in soft tissue, internal organs, brain, or eye.^{90,92,93} Diagnosis is made by biopsy with characteristic histiocytes that stain with macrophage markers, including CD68, factor XIIIa, and fascin. “Touton giant cells,” vacuolated, foamy histiocytes with multiple nuclei, are classic but not universally present. Biopsies may also include spindle-shaped cells resembling benign fibrous histiocytoma with foamy histiocytes.⁹⁰ Physical examination and laboratory and imaging studies are required to differentiate skin-limited from systemic JXG.

In most cases, patients with skin-limited disease do not require therapy and lesions resolve over time. Systemic JXG, like high-risk LCH, may be lethal. Strategies effective in LCH have been reported as effective in JXG.⁹⁴ Cladribine and clofarabine have been reported as effective in patients with refractory or recurrent disease in case reports and case series.^{87,95}

Erdheim-Chester disease—ECD is an extremely rare disease that is histologically indistinguishable from JXG but arises in characteristic clinical patterns in adults. Lesions may arise in virtually any organ system, but osteosclerosis of the leg bones, perirenal infiltration resulting in a “hairy” rind on kidneys on MRI, and formation of fibrotic sheath around the aorta are characteristic. The mean survival of ECD patients remains less than 3 years. As in LCH, somatic mutations in *BRAF-V600E* are common in ECD.⁷⁷ Therapies have included interferon- α , blocking of inflammatory signals with targeted agents, and more recently, vemurafanib in patients with the *BRAF-V600E* mutation.^{88,96}

Malignant histiocytosis—Malignant histiocytosis (also described as histiocytic sarcomas) describes a group of conditions with cells resembling macrophages or DCs that have biological and histologic features of malignant cells. This diagnosis is largely a diagnosis of exclusion, with ALCL and other T-lineage and B-lineage large cell lymphomas ruled out.⁹⁷ Increasing cases of “transdifferentiation” between lymphoid malignancies and malignant histiocytic diagnoses are being reported, which likely reflect parallel differentiation from a common transformed precursor cell.^{98–100}

Rosai-Dorfman disease—Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is an intriguing and still poorly understood phenomenon of apparently nonmalignant proliferation of histiocytes generally restricted to lymph nodes.¹⁰¹ However, extranodal lesions may also be observed, most often as subcutaneous nodules, sinus lesions, or bone lesions. The classic clinical presentation, as

noted by disease nomenclature, is massive painless bilateral cervical lymphadenopathy. Biopsies demonstrate infiltration of lymph nodes with histiocytes with emperipolesis, the trafficking of viable lymphocytes through the phagocyte. The histiocytes stain for typical macrophage markers including CD68 and CD14.¹⁰² Most cases are self-limiting, but lymphadenopathy may cause potential harm through mass effect on vital structures. Many agents used in lymphoma and LCH have been reported to have temporizing effects on RDD lesions, although the lymph nodes typically rebound after discontinuation of therapy. Some patients with refractory bone and CNS lesions were effectively treated with clofarabine.⁸⁷ It should be noted that the frequent nonspecific histologic description of lymph nodes having “sinus histiocytosis” is distinct from RDD.

Hemophagocytic lymphohistiocytosis—Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of pathologic activation of macrophages and T cells that results in end-organ damage. There are numerous causes that lead to this phenomenon, including inherited defects of cytotoxic lymphocyte function, infections, persistent antigen stimulation in the setting of autoimmune disease, malignancies with antigen-presenting function, and iatrogenic derangement of normal immune function due to chemotherapy or bone marrow transplant (reviewed in¹⁰³). Germline mutations in genes encoding proteins involved in cytotoxic function of NK cells and lymphocytes, including PRF1, MUNC13-4, AP3, LYST, Rab27a, STX11, and STXBP2, can cause “familial” HLH and typically arises in young children (reviewed in¹⁰⁴). “Secondary” HLH is a term used to describe pathologic inflammation associated with an antigen trigger, such as malignancy or autoimmune disease, and may occur at any age. However, the line between presumed familial and secondary or acquired HLH is becoming increasingly blurred with the discovery of hypomorphic, heterozygous, or compound heterozygous mutations in HLH-associated genes in patients with “secondary” HLH.^{105–107}

The finding of “hemophagocytosis” or engulfment of erythrocytes (and leukocytes) by activated macrophages for which HLH is named is neither sensitive nor specific for HLH. Diagnosis is made by a series of clinical criteria,^{103,108} followed by investigations for the causes of the pathologic inflammation. When unrecognized and untreated, HLH is generally fatal. Therapy consists of immune suppression, and in cases of fixed immune defects or intractable pathologic inflammation, HSCT. Outcomes for patients with presumed familial or secondary HLH were not different in the HLH-94 clinical trial. Immune suppression with etoposide and dexamethasone, according to HLH-94, is generally considered the standard of care for initial treatment of patients with HLH.¹⁰⁹ Although differentiating stochastic immune challenges from inherited, fixed immune defects is important in determining whether a patient ultimately requires stem cell transplant, this distinction is not as significant in managing inflammation in the acute setting. In contrast to the diseases discussed with the possible exception of RDD, HLH is not a neoplastic condition, rather it represents induced pathologic function in histiocytes (macrophages).

SUMMARY

Although there have been dramatic improvements in the treatment of children with lymphoma, approximately 25% of children will still relapse or fail to respond to initial

therapy. In addition, late effects remain a concern. The identification of both clinical and biologic features at the time of diagnosis that predict treatment failure will enable investigators to refine existing risk-adapted therapeutic approaches. Strategies to be considered for children at high risk for treatment failure include the intensification of existing regimens and the incorporation of new active or novel agents. Novel approaches include the incorporation of immunotherapeutic agents into multi-agent chemotherapy regimens. For example, there is increasing experience with the anti-CD20 and anti-CD30 antibodies,²⁸ including radiolabeled forms. Novel immunotherapeutic approaches using cytotoxic T lymphocytes for EBV-associated lymphomas as well as gene-modified T cells using the CAR-CD19 are also entering advanced phase trials.^{110–112} Finally, agents targeting specific molecular lesions (eg, the *ALK* inhibitor for ALCL) are promising and being studied in combination with standard chemotherapy. Comprehensive molecular characterization of childhood lymphomas is also essential and may help to further refine disease classification, provide a means of detecting minimal residual disease during clinical remission, and enhance the assessment of early response. Recognition of the long-term toxicities of therapy is still a major driving principle for the development of new approaches.

Progress in improving outcomes for patients with histiocytic disorders has been challenged by ambiguous classification of the diseases as inflammatory versus malignant as well as organizational and biological obstacles to translational research efforts. Recent advances in understanding the pathogenesis of LCH include identification of recurrent mutations in *BRAF-V600E* and localization of somatic mutations to hematopoietic stem cells in patients with high-risk disease.^{74,78} The functional importance of activation of MAPK pathway by *BRAF-V600E* is supported by the ability to recapitulate a high-risk LCH-like phenotype in mice in which *BRAF-V600E* expression is enforced in early myeloid lineages, as well as by promising responses in early case series of patients with combined LCH/ECD treated with vemurafenib (*BRAF* inhibition).^{74,78} Together, these findings have philosophic significance in supporting reclassification of LCH (and by extension JXG and ECD) as myeloid neoplastic diseases. Practically, these advances support further investigation of novel approaches to diagnosis, risk-stratification, and therapy. The pace of improvements for patients with histiocytic disorders will be accelerated by enhanced support for preclinical translational research as well as cooperative clinical trials.

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KEY POINTS

- Non-Hodgkin lymphoma (NHL) accounts for approximately 7% of cancers in patients less than 20 years of age, or approximately 800 cases annually in the United States.
- With current therapies based on histology, cure rates of NHL range from 65% to more than 90%, even for disseminated disease.
- A major challenge that needs to be overcome is to optimize up-front treatment of NHL to prevent relapse because prognosis for patients with refractory of relapsed disease remains exceedingly poor.
- Another major objective for NHL therapy development is to use novel targeted therapies not only to improve outcomes for patients but also to decrease bystander organ toxicities and late effects.

Table 1
Major histopathological categories of non-Hodgkin lymphoma in children and young adults

Category (WHO Classification/Updated REAL)	Category (Working Formulation)	Immunophenotype	Clinical Presentation	Chromosome Translocation	Genes Affected
BLs	Malignant lymphoma small noncleaved cell	Mature B cell	Sporadic: head and neck (not jaw), intra-abdominal, bone marrow, CNS Endemic: >50% head and neck (jaw)	t(8;14) (q24;q32), t(2;8) (p11;q24), t(8;22) (q24;q11)	<i>C-MYC</i> , <i>IGH</i> , <i>IGK</i> , <i>IGL</i>
DLBCL	Malignant lymphoma large cell	Mature B cell; occ CD30+	Nodal, abdominal, bone, and mediastinal Primary CNS generally associated with immunodeficiency	No consistent cytogenetic abnormality identified except in PMBL	PMBL: gains in chromosome 9p and 2p in regions that involve <i>JAK2</i> and <i>c-rel</i> <i>SOCS1</i> inactivation
ALCL (systemic)	Malignant lymphoma immunoblastic or malignant lymphoma large cell	CD30+ (Ki-1+) T cell or null cell	Variable, systemic symptoms often prominent	t(2;5) (p23;q35); less common variant translocations involving <i>ALK</i>	<i>ALK</i> , <i>NPM</i>

Table 2

French-American-British/LMB staging schema for B-cell non-Hodgkin lymphoma

	Stratum	Disease Manifestation
FAB/LMB International Study ^{30,113,114}	A	Completely resected stage I and abdominal stage II
	B	Multiple extra-abdominal sites Nonresected stage I and II, III, IV (marrow <25% blasts, no CNS disease)
	C	Mature B-cell ALL (>25% blasts in marrow) and/or CNS disease

Abbreviations: ALL, acute lymphoblastic leukemia; FAB, French-American-British.

Table 3

Standard treatment options for low-stage non-Hodgkin lymphoma

Disease	Treatment Options	Outcomes
BL or DLBCL (completely resected)	BFM-90/95 (R1): 2 cycles of chemotherapy ¹⁰	EFS >95%
	COG-C5961 (FAB/LMB-96) (group A): 2 cycles of chemotherapy ¹¹⁴	
BL or DLBCL (nonresected stage I/II)	BFM-95 (R2): Prephase + 4 cycles of chemotherapy (4-h methotrexate infusion) ¹⁰	EFS 95%
	COG-C5961 (FAB/LMB-96) (group B): prephase + 4 cycles of chemotherapy (reduced-intensity arm) ³⁰	EFS 98%
ALCL	POG-8314/POG-8719: 3 cycles of CHOP ²⁶	EFS 88% for DLBCL and ALCL (5 y)
	BFM-90: prephase + 3 cycles of chemotherapy (only for completely resected disease) ¹¹⁵	90% EFS
	ALCL99: prephase + 6 cycles of chemotherapy (for disease not completely resected) ¹¹⁶	Completely resected patients: 100% EFS Patients without complete resection: EFS 81% (3 y)

Abbreviations: BFM, Berlin-Frankfurt-Munster; FAB, French-American-British.

Table 4

Standard treatment options for high-stage B-cell non-Hodgkin lymphoma

Disease Stage	Disease Manifestations	Regimen	Outcome
FAB/LMB-96 International Study COG-C5961 ^{30,113}	B Multiple extra-abdominal sites Nonresected stage I, II, III, IV Marrow <25% blasts No CNS disease	Prephase + 4 cycles of chemotherapy (reduced intensity arm) ³⁰	90%–94% 4 y EFS (70% PBML)
	C Mature B-cell ALL (>25% blasts in marrow) and/or CNS disease	Prephase + 8 cycles of chemotherapy (full intensity arm) ¹¹³	70%–90% EFS Best responders if in CR after 3 cycles standard intensity treatment 70% EFS in patients with CNS disease
BFM Group^{10,117}			
R2	Nonresected stage I/II and stage III with LDH <500 IU/L	Prephase + 4 cycles of chemotherapy (4 h methotrexate infusion) ¹⁰	EFS >95%
R3	Stage III with LDH 500–999 IU/L Stage IV, B-cell ALL (>25% blasts) and LDH <1000 IU/L No CNS disease	Prephase + 5 cycles of chemotherapy (24 h methotrexate infusion) ¹⁰	Overall EFS 85% for R3 Overall EFS 81% for R4 Reducing MTX from 24 to 4 h → inferior outcome (75 vs 91% EFS)
R4	Stage III, IV, B-cell ALL with LDH >1000 IU/L Any CNS disease	Prephase + 6 cycles of chemotherapy (24 h methotrexate infusion) ¹⁰	PMBL: 50% EFS (3 y) CNS presentation: 70% EFS (3 y)

Abbreviations: ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Munster; LDH, lactate dehydrogenase.

Table 5
Variability in risk stratification across pediatric Hodgkin lymphoma clinical trials consortia

	Risk	IA	IB	IIA	IIB	IIIA	IIIB	IVA	IVB
EuroNet C1	Low								
	Int	E	E	E					
	High				E	E			
COG	Low								
	Int	E		E					
	High	X		X					
St Jude Stanford DFCl	Low								
	Int	E		E					
	High	mX		mX >2					

Abbreviations: E, extranodal extension; Int, intermediate; mX, mediastinal bulk; X, bulky disease (peripheral >6 cm and mediastinal).

Table 6

Results of recent trials for pediatric low-risk Hodgkin lymphoma

Group	Study	n	LR Definition	Chemotherapy	RT (Dose, Field)	EFS or DFS, OS (y)
Europe						
French Society of Pediatric Oncology ¹¹⁸	MDH90	202	IA, IB, IIA, IIB	VBVP × 4 (+OPPA × 1–2 if PR after cycle 4)	20–40 Gy IF	91.1%, 97.5% (5 y)
German Society of Pediatric Oncology and Hematology	GPOH-HD-95 ¹¹⁹	328	IA, IB, IIA	OPPA (F); OEPA (M) × 2	CR after cycle 2: no RT PR after cycle 2: 20–30 Gy IF	93.2%, 98.8% (10 y)
	GPOH-HD-2002 ⁶⁰	195	IA, IB, IIA	OPPA (F); OEPA (M) × 2	CR after cycle 2: no RT PR after cycle 2: 20–30 Gy IF	92%, 99.5% (5 y)
North America						
Stanford, Dana Farber, St Jude consortium	¹²⁰	110	IA, IB, IIA, IIB no bulk, no E	VAMP × 4	15–22.5 Gy IF	89.4%, 96.1% (10 y)
	¹²¹	88	IA, IIA, <3 nodal sites, no bulk, no E	VAMP × 4	CR after cycle 2: no RT PR after cycle 2: 25.5 Gy IF	EFS: 90.8% (2 y)
CCG, POG, and COG	CCG 594 ²⁵⁹	294	IA, IB, IIA without adverse features ^a	COPP/ABV × 4	CR after cycle 4: randomized to 21 Gy IFRT vs no RT PR: 21 Gy IF	10 y EFS IFRT: 100% No RT: 89.1% (<i>P</i> = .001) 10 y OS: RT: 97.1% No RT: 95.9% (<i>P</i> = .5)
	P9426 ¹²²	294	IA, IB, IIA, IIIA	DBVE × 2–4 (based on response after cycle 2)	25.5 Gy IF	86.2% 97.4% (8 y)
	AHOD0431 ⁴⁶	287	IA, IIA, no bulk	AV-PC × 3	CR after cycle 3: no RT PR after cycle 3: 21 Gy IF	79.8% 99.6% (4 y)

Abbreviations: AV-PC, doxorubicin, vincristine, prednisone, cyclophosphamide; COPP/ABV, cyclophosphamide, bleomycin, vinblastine, CR, complete response; DBVE, doxorubicin, bleomycin, vincristine, etoposide; DFS, disease-free survival; EFS, event-free survival; F, female; IF, involved field; LR, M, male; OEPA, vincristine, etoposide, prednisone, doxorubicin; OPPA, vincristine, procarbazine, prednisone, doxorubicin; OS, overall survival; PR, partial response; RT, radiation therapy; VAMP, vinblastine, doxorubicin, methotrexate, prednisone; VBVP, vinblastine, bleomycin, etoposide, prednisone.

^a Adverse features = hilar disease, bulk, 4 nodal regions, mediastinal tumor.

Table 7

Results of recent trials for pediatric intermediate and high-risk Hodgkin lymphoma

Group	Study	N	Definition	Chemotherapy	RT (Dose, Field)	EFS or DFS, OS (y)
Europe						
German Society of Pediatric Oncology and Hematology	GPOH-HD-95 ¹¹⁹	341	Intermediate: I _E A/B; II _E A; IIB; IIIA High: II _E B; III _E A/B; IIIB; IV	2 OPPO/OEPA + 4 COPP.	CR after cycle 2: no RT PR after cycle 2: 20–35 Gy IF	84.5%, 93.2% (10 y)
	GPOH-HD-2002 ⁶⁰	Intermediate: 139 High: 239	Intermediate: I _E A/B; II _E A; IIB; IIIA High: II _E B; III _E A/B; IIIB; IV	OPPO (F); OEPA (M) × 2 Intermediate: COPDAC × 2 High: COPDAC × 4	19.8–35 Gy IF	Intermediate: 88.3%, 99.5% High: 86.9%, 94.9% (5 y)
North America						
CCG, POG, and COG	CCG 5942 ⁵⁹	Intermediate: 394 High: 141	Intermediate: IA, IB, IIA with adverse features ^a ; IIB, III High: IV	Intermediate: COPP/ABV × 6 High: COPP/ABV, CHOP, Etoposide/Cytarabine × 2	CR after cycle 6: randomized to 21 Gy IFRT vs no RT PR: 21 Gy IF	Intermediate: RT: 87%, 95% No RT: 83%, 100% High: RT: 90%, 100% No RT: 81%, 94% (EFS) <i>P</i> < .05
	P9425 ¹²²	Intermediate: 53 High: 163	Intermediate: IB, IIA _{LMA} , IIIA High: IIB, IIIB, IV	DBVE-PC × 3–5 (based on response after cycle 3)	25.5 Gy IF	Intermediate: 84%, OS NR High: 85%, OS NR (5 y)
	C59704 ¹²³	99	IIB/IIIB + bulk, IV	BEACOPP × 4 M RER: ABVD × 2 F RER: COPP/ABV × 4 SER: BEACOPP × 4	M RER: 21 Gy IF F RER: No RT SER: 21 Gy IF	94%, 97% (5 y)
	AHOD0031 ⁴⁶	1712	IA, IIA + bulk, IB, IIB, IIIA, IVA	ABVE-PC × 4 SER: randomized DECA × 2	Randomized RER after cycle 2 and CR after cycle 4: no RT All others: 21 Gy IF	85.6%, 98.2% (3 y)

Abbreviations: ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; COPDAC, cyclophosphamide, vincristine, prednisone, dacarbazine; COPP/ABV, cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine; CR, complete response; DBVE-PC, doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; DECA, dexamethasone, etoposide, cisplatin, cytarabine; F, female; IF, involved field; M, male; OEPA, vincristine, etoposide, prednisone, doxorubicin; OPPO, vincristine, procarbazine, prednisone, doxorubicin; PR, partial response; RER, rapid early responder; RT, radiation therapy; SER, slow early responder.

^a Adverse features = hilar disease, bulk, 4 nodal regions, mediastinal tumor.

Table 8

Differentiating characteristics of histiocytes

Histologic Features	LCH	Malignant Histiocytosis	ECD/JXG	HLH	RDD
HLH-DR	++	+	-	+	+
CD1a	++	+/-	-	-	-
CD14	-	+/-	++	++	++
CD68	+/-	+/-	++	++	++
CD163	-	-	+	++	++
CD 207 (Langerin)	+++	+/-	-	-	-
Factor XIIIa	-	-	++	-	-
Fascin	-	+/-	++	+/-	+
Birbeck granules	+	+/-	-	-	-
Hemophagocytosis	+/-	+/-	-	+/-	-
Emperipolesis	-	-	-	-	+

Adapted from Refs. 124–126