Pediatric Langerhans Cell Histiocytosis: State of the Science and Future Directions

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Abstract: Langerhans cell histiocytosis (LCH) is an inflammatory neoplasm of myeloid origin characterized by the presence of classic CD1a+/CD207+ cells. An ongoing debate over the grouping of LCH was finally settled in favor of neoplasm after the discovery of the BRAF V600E mutation in 2010. The pathologic cells were found to involve an almost universal activation of the MAPK/ERK pathway, with mutations identified in most kinases upstream of ERK (RAS/RAF/MEK). The clinical presentation of LCH is a mixed bag, ranging from self-resolving localized disease to fulminant, fatal disseminated disease. The current standard of care for patients with multisystem LCH, who have high relapse rates, continues to be combination treatment with vinblastine and prednisone. Patients treated with BRAF and MEK inhibitors have shown a significant and sustained response in early-phase trials. During the current decade, researchers have described an extensive genomic landscape for LCH that has significantly enlarged our understanding of the biology and pathogenesis of this disease, especially neurodegenerative LCH. These advances have opened the door to studies of precision medicine and targeted therapy in LCH. Disease reactivation, long-term sequelae, very high-risk disease, and neurodegenerative LCH represent ongoing challenges. A renewed understanding of the biology of this disease, coupled with targeted therapies, may help in overcoming most of these challenges.

Introduction

Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasm that can affect both children and adults. It is characterized by the accumulation of pathologic Langerhans cells, commonly in the bones, skin, liver, spleen, lungs, bone marrow, and brain. LCH is a rare disease, affecting 4 to 8 children per million and 1 to 2 adults per million—an incidence similar to that of pediatric Hodgkin lymphoma.1-5 The clinical features of LCH are highly heterogeneous, ranging from localized self-resolving disease to fulminant, disseminated, and leukemia-like forms.6

The initial description of the disease can be traced back to Hippocrates, who in 400 BCE described painful skull lesions in a patient who presumably had LCH.7 In the early 1900s, various
forms of LCH were branded as Hashimoto-Pritzker disease, eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease. Finally, in 1953, Lichtenstein unified the various forms of LCH under the label histiocytosis X, in which the “X” referred to a cell of uncertain origin. In 1973, Nezelof and colleagues identified Birbeck granules in histiocytosis X cells with the help of electron microscopy, thereby replacing unknown “X” with Langerhans cells. In this review, we discuss the most recent biological discoveries relevant to this enigmatic and rare neoplastic disorder, along with the treatment implications of the findings.

**Pathogenesis and Biology**

The question of whether LCH is caused by immune dysregulation or is neoplastic in nature has been a topic of debate for decades. The disease may present as a single, localized lesion that resolves on its own or responds to anti-inflammatory therapy, features compatible with an immune dysregulation process. In other cases, the disease is widely disseminated at presentation and associated with significant mortality; the use of chemotherapy is required, which suggests a neoplastic etiology.

The classic CD1a+/CD207+ pathologic cells account for less than 10% of the histology in LCH; a polymorphic inflammatory infiltrate characterizes most of the histologic milieu. The pathologic Langerhans cells are in an activated state, as indicated by the presence of diverse inflammatory cytokines and the expression of CD40, highlighting the interaction with T cells and strengthening the inflammatory/immune theory. The most robust previous evidence supporting the neoplastic theory was a demonstration of clonality of Langerhans cells by the X-linked human androgen receptor gene (HUMARA) assay. Clonality alone, however, especially in immune cells, would not be sufficient evidence to classify a disease as a malignancy in the absence of a genetic abnormality conferring a survival advantage by affecting the proliferative or apoptotic pathway. The lack of adequate evidence was reflected in one of the first publications by the Histiocyte Society on the classification of histiocytosis, which stated that “there is no evidence that the disease is a malignant neoplastic process.”

The landscape of histiocytic disorders changed in 2010 with the identification of various genetic abnormalities, first in LCH and later across the entire spectrum of histiocytic disorders. These discoveries contributed significantly to our understanding of the disease and its pathogenesis at the molecular level, leading the World Health Organization to define LCH as “a clonal neoplastic proliferation of Langerhans-type cells.” The discoveries also led to a newer classification of histiocytic disorders and initiated an era of targeted therapy in LCH. The landmark publication by Dr Barrett Rollins’ group in 2010 was historic for 2 reasons. This publication was the first to identify BRAF V600E mutations in nearly 60% of archived LCH samples, establishing the genetic abnormality and classifying LCH as part of the neoplastic group of diseases. In addition, it demonstrated universal immunostaining of phospho-MEK and phospho-ERK regardless of BRAF status, suggesting a constitutively active mitogen-activated protein kinase (MAPK) pathway across LCH. This finding opened the door for the identification of other genomic alterations leading to ERK activation in the absence of a BRAF mutation.

**MAPK Pathway Activation**

Reviewing the MAPK pathway is fundamental to understanding the pathogenesis of LCH. The MAPK pathway is one of those frequently mutated in human cancer. It couples extracellular signals to intracellular machinery that controls cell growth, proliferation, and differentiation. Extracellular signaling is finally transmitted to the nucleus for the activation of transcription via a downstream cascade consisting of RAS to RAF to MEK to ERK. BRAF is a member of the RAF family and is activated by RAS proteins and RAS-coupled receptor tyrosine kinases. MAP2K1 (also known as MEK1) is downstream of the RAF family and is responsible for ERK1/2 activation. The nearly universal ERK activation in LCH implies the presence of an activating mutation in any of the upstream components of—or other pathways that cross-talk with—the MAPK pathway, leading to ERK activation directly or indirectly. A systematic search has identified mutations in almost all the kinases upstream of ERK and the cross-talking pathways (Table 1). The mutations in the cascade can best be grouped according to the kinase they activate—that is, RAF-, MEK-, and non–RAF/MEK-activating mutations. BRAF- and MEK-activating mutations are the only recurrent mutations that have been identified in 50% to 60% and 10% to 30% of LCH cases, respectively. The rest of the mutations in the MAPK pathway have been reported in single case reports or small series.

**RAF-Activating Mutations.** The RAF kinases (ARAF, BRAF, and CRAF) constitute a family of serine/threonine kinases that play a central role in the MAPK (RAS/RAF/MEK/ERK) pathway by transducing mitogenic signals from the cell membrane to the nucleus. Of these, BRAF is the most frequently mutated in human cancers, with the BRAF V600E mutation alone accounting for 90% of activating BRAF mutations. The BRAF V600E activating mutation (substitution of glutamate by valine...
THACKER AND ABLA

at amino acid 600) leads to RAS-independent activation of the MEK/ERK signaling cascade and is found in 50% to 60% of LCH cases. In addition to the classic BRAF V600E mutation, other BRAF mutations, such as V600D, V600insDLAT, G466R, del exon 12, and splicing mutations, have been described in single case reports. Although some of them are known to be activating mutations, further functional assessment is required for others. At least 2 ARAF mutations have been described in LCH. These include a compound-activating mutation that is sensitive in vitro to vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) and an ARAF T70M mutation that occurs together with BRAF V600E. ARAF mutations have been found in increased frequencies in other histiocytic disorders.

The data regarding the clinical significance of BRAF mutations are contradictory. In a retrospective French cohort of 315 patients, a somatic BRAF V600E mutation was found in 55% of patients. The frequency of BRAF mutations in the high-risk LCH group (88%) was twice that in the low-risk group (44%). On multivariate analysis, BRAF mutations were found to be independently associated with risk for organ involvement. The number of poor responders to frontline therapy, the reactivation rate, and the number of patients with permanent long-term sequelae were higher in the BRAF-mutant cohort than in the nonmutant cohort.

MEK-Activating Mutations. MAP2K1 encodes the MAP kinase MEK1, leading to constitutive activation of the pathway. It is the second most commonly mutated gene after BRAF, identified in 10% to 30% of LCH cases. Mutations in MAP2K1 and the BRAF V600E mutation are mutually exclusive.

Non–RAF/MEK-Activating Mutations. Somatic mutation in NRAS has been reported in a single case of juvenile myelomonocytic leukemia with LCH. On the basis of a clinical response to a pan-AKT inhibitor, a search for the PIK3CA mutation yielded a mutation in only one case. Single cases of a mutation in PIK3R2, PICK1, or ERBB, with a possible role in ERK activation, have been reported. To put it in context, PI3K pathways cross talk with MAPK pathways downstream of MEK. Like ERK activation, tumor protein p53 (TP53) overexpression is almost universally observed in LCH. Although this finding suggests the possibility of abnormality in the TP53 pathway, only one case with a mutation in TP53 has been identified thus far.

Cell of Origin and Disease Severity

For years, LCH was believed to arise from immature epidermal Langerhans cells that proliferated as a result of

<table>
<thead>
<tr>
<th>RAF mutations</th>
<th>BRAF mutations</th>
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<tr>
<td>Missense</td>
<td>In-frame deletions/insertions</td>
</tr>
<tr>
<td>ARAF</td>
<td>Missense</td>
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<tr>
<td>MEK mutations</td>
<td>MAP2K1</td>
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<tr>
<td>MAP3K1</td>
<td>Missense</td>
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<tr>
<td>RAS mutations</td>
<td>NRAS</td>
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<tr>
<td>KRAS</td>
<td>Other</td>
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p., position.
Durham BH. Semin Cell Dev Biol. 2018;S1084-9521(17)30364-6;17
inflammatory/immune activation, giving rise to lesions in various organs. According to this “activated-immature” model, T cells had no interactions with Langerhans cells. The model was challenged in 2014 with the “mis-guided myeloid dendritic cell precursor” model of Allen and colleagues, who suggested that pathologic cells in LCH develop from bone marrow–derived myeloid/dendritic cell precursors that subsequently acquire CD207 antigen as they home into disease sites. Gene expression profiling of pathologic cells in LCH showed their profile to be closer to that of immature myeloid dendritic cells than of epidermal Langerhans cells. Additionally, lineage analysis of peripheral blood mononuclear cells (PBMCs) in high-risk patients traced the \( \text{BRAF} \ V600E \) mutation to monocytes (CD14+) and myeloid dendritic cells (CD11c+), confirming the myeloid origin of LCH cells. In a search further upstream, the CD34+ hematopoietic stem cells of only high-risk patients exhibited \( \text{BRAF} \ V600E \), whereas the mutation was not found in cord blood samples, suggesting that the mutation is acquired later.

In a mouse model, expression of the \( \text{BRAF} \ V600E \) mutation in langerin-positive cells gave rise to localized LCH-like lesions without mutations in circulating cells. In contrast, expression of \( \text{BRAF} \ V600E \) in CD11c+ cells led to an aggressive disease phenotype similar to that of disseminated high-risk LCH, highlighting that disease severity depends on the developmental stage of the myeloid cell in which the mutation occurs. An activating mutation in a tissue-restricted mature cell would give rise to low-risk LCH, whereas a mutation in a hematopoietic stem cell or an immature myeloid dendritic cell would manifest as high-risk, disseminated LCH. This constitutes the “mis-guided myeloid differentiation model,” which is reinforced by the presence of a \( \text{BRAF} \ V600E \) mutation in the PBMCs of all patients with \( \text{BRAF} \)-mutant high-risk LCH, 13% of patients with low-risk (multisystem) LCH, and no patients with single-system LCH.

Revised Classification

The first classification of histiocytoses was published in 1987, when LCH was not considered a neoplasm. Histiocytoses were divided into 3 groups: Langerhans cell histiocytosis, non–Langerhans cell disorders, and malignant histiocytosis. With recent advances in molecular research, histiocytic disorders earned a new classification, recommended in 2016. Histiocytic disorders are now divided into 5 groups on the basis of clinical, radiographic, pathologic, phenotypic, genetic, and/or molecular features: the L (Langerhans) group, the C (cutaneous and mucocutaneous histiocytoses) group, the H (hemophagocytic lymphohistiocytosis and macrophage activation syndrome) group, the R (Rosai-Dorfman disease, miscellaneous noncutaneous, non-Langerhans cell histiocytoses) group, and the M (malignant histiocytoses) group.

The discovery of the \( \text{BRAF} \) mutation helped to establish a link between Erdheim-Chester disease (ECD) and LCH, with nearly 20% of patients who had ECD also demonstrating LCH lesions. Additionally, the 2 conditions share genetic mutations in the MAPK pathway and have similar clinical complications. The recent classification therefore proposes to include LCH, ECD, mixed ECD/LCH, and extracutaneous juvenile xanthogranuloma in the L group.

Clinical Manifestations

The clinical manifestations of LCH depend on the organ involved and the extent of involvement. Involvement of almost every organ, with the exception of the gonads and kidneys, has been described in the literature. Bone is the most commonly involved organ; bony involvement is present in 80% of cases, and a painful bony lesion is the most common presentation. Skin is the second most frequently involved organ; the presentation may be a rash (generalized, papular, ulcerative, or vesicular) and/or seborrheic involvement of the scalp. Features of weight loss, diarrhea, edema, dyspnea, jaundice (conjugated hyperbilirubinemia), cytopenias, hepatosplenomegaly, lymphadenopathy, polydipsia, and polyuria indicate specific organ involvement. Involvement of the central nervous system (CNS) in LCH is varied and discussed in detail later.

Owing to its heterogenous presentation, from limited, self-resolving disease to a disseminated form associated with mortality, LCH over the years has been clinically classified according to the number of lesions and sites of involvement coupled with the number of specific poor-risk organs affected. This classification, in combination with an assessment of the response to treatment, is the basis of risk-adapted therapy for LCH. At present, cases of LCH are risk-stratified according to extent of disease (single system vs multisystem); risk-organ involvement (presence or absence of involvement of the liver, spleen, or bone marrow), in which “risk” refers to risk for mortality; and early response to therapy (an inadequate response at 6 weeks has been shown to be a poor prognostic factor) (Table 2). At present, data regarding the role of \( \text{BRAF} \ V600E \) in risk stratification and prognosis are conflicting, owing to limited numbers and retrospective data. However, a role for the stratification of LCH on the basis of a combination of molecular, clinical, and response criteria may be possible in the future.
process.32,33 However, recent work has added new insights of a neuro-inflammatory, paraneoplastic autoimmune CNS disease after systemic cure generated the hypothesis cells in brain biopsy specimens and the presentation of the classic CD1a+ cells. The absence of pathologic LCH of the CNS can present as neurodegenerative disease (ND-LCH) and/or intracranial tumorous lesions. Diabetes insipidus is the most common presentation, affecting one-quarter of patients who have LCH. ND-LCH affects 5% of patients who have LCH, with an incidence as high as 24% in population-based studies. The pathology of diabetes insipidus and the tumorous lesions is straightforward, and the histology is consistent with that of extracranial LCH lesions.32,33

ND-LCH is a syndrome of progressive, devastating neurodegeneration of unknown etiology. One of the most intriguing of entities, its severity and course are variable. Recent efforts have been made to rename ND-LCH as “LCH-associated CNS imaging” (LACI) or “LCH-associated CNS symptoms” (LACS) to reduce the anxiety associated with the term neurodegenerative.35 The presentation may be concurrent with that of systemic LCH or take place up to a decade after LCH has been cured. The discordance observed between the clinical symptoms (LACS) and the imaging findings (LACI) is considerable; one can occur without the other, and the severity of one does not necessarily reflect the severity of the other. Patients with CNS-risk bone involvement, diabetes insipidus, or CNS tumorous lesions are at increased risk for LACI/LACS. On histologic analysis, LACI/LACS lesions strikingly lack the classic CD1a+ cells. The absence of pathologic LCH cells in brain biopsy specimens and the presentation of CNS disease after systemic cure generated the hypothesis of a neuro-inflammatory, paraneoplastic autoimmune process.32,33 However, recent work has added new insights into our understanding of LACI/LACS and may change our approach to its management. BRAFV600E DNA was detected in the cerebrospinal fluid of only 10% of patients with ND-LCH; however, it was found significantly more frequently in the PBMCs of patients in whom ND-LCH developed at all stages of therapy. Brain biopsy specimens of patients with ND-LCH demonstrated diffuse perivascular infiltration by BRAF V600E cells, which were CD207-negative with a monocyte phenotype and associated with osteopontin expression in the areas corresponding to changes on T2-weighted magnetic resonance imaging. These findings suggested that ND-LCH might be an active disease process as opposed to a paraneoplastic or autoimmune one. Among patients who had ND-LCH treated with a BRAF V600E inhibitor, 75% demonstrated significant clinical and radiologic improvement, indicating the efficacy of a novel approach to treatment.34

Central Nervous System LCH

LCH of the CNS can present as neurodegenerative disease (ND-LCH) and/or intracranial tumorous lesions. Diabetes insipidus is the most common presentation, affecting one-quarter of patients who have LCH. ND-LCH affects 5% of patients who have LCH, with an incidence as high as 24% in population-based studies. The pathology of diabetes insipidus and the tumorous lesions is straightforward, and the histology is consistent with that of extracranial LCH lesions.32,33

Table 2. LCH Clinical Classification and Risk Stratification

<table>
<thead>
<tr>
<th>Involved System, Risk</th>
<th>Involved Organ/Response</th>
</tr>
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<tbody>
<tr>
<td>Single system, unifocal or localized</td>
<td>1 lesion in 1 organ</td>
</tr>
<tr>
<td>Single system • Multifocal • Special site</td>
<td>≥2 lesions in 1 organ or in a special site¹</td>
</tr>
<tr>
<td>Multisystem, low risk</td>
<td>≥2 organs involved without risk-organ² involvement</td>
</tr>
<tr>
<td>Multisystem, high risk</td>
<td>Any risk-organ³ involvement</td>
</tr>
<tr>
<td>Multisystem, very high risk</td>
<td>Risk-organ involvement and lack of response to 6 weeks of standard treatment</td>
</tr>
</tbody>
</table>

¹ Special sites are intracranial soft-tissue extension or vertebral lesions with intraspinal soft-tissue extension.
² Risk organs are the liver, spleen, and hematopoietic system.
³ Risk-organ involvement and lack of response to 6 weeks of standard treatment.

Our knowledge of LCH and its pathogenesis has lagged behind clinical experience and therapy. On the basis of principles learned during the treatment of acute lymphoblastic leukemia, LCH has been treated with vinca alkaloids and corticosteroids since the 1960s.35 After half a century, these continue to be the backbone of frontline therapy in LCH. Since the 1980s, the Histiocyte Society has been conducting cooperative international trials based on risk stratification, which have led to the evolution of LCH treatment over decades. The current principles of LCH therapy are based on experience from previous cooperative trials—namely, the German and Austrian DAL-HX studies, the Histiocyte Society LCH-I, -II, and -III trials, and the Japanese trials36-42 (Table 3). The last Histiocyte Society trial, LCH-III, established 12 months of therapy with vinblastine and prednisone as standard therapy for high-risk multisystem LCH (MS-LCH) and showed no benefit from the addition of methotrexate. Increasing the duration of therapy from 6 to 12 months in low-risk MS-LCH significantly reduced the risk for reactivation. The Japanese LCH Study Group trial, JSLG-02, demonstrated outcomes comparable with those of LCH-III for vincristine/prednisolone/cytarabine–based induction and 48 weeks of multiagent continuation therapy. The prolongation of induction therapy to 12 weeks for patients with an inadequate response and an early switch to salvage therapy (at 6 weeks) for those with progressive disease seem to improve outcomes.

First-Line Therapy

The ongoing Histiocyte Society trial, LCH-IV, has 7 strata of therapy. Stratum 1 is testing in a randomized fashion to assess if therapy prolongation (to 24 months) and intensification (with 6-mercaptopurine) can further improve outcomes for high-risk patients. This stratum will also evaluate the benefit of prolonging therapy from...
### Table 3. Major Findings From the Histiocyte Society International Trials

<table>
<thead>
<tr>
<th></th>
<th>LCH-I</th>
<th>LCH-II</th>
<th>LCH-III</th>
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<tbody>
<tr>
<td>N</td>
<td>143</td>
<td>193</td>
<td>422</td>
</tr>
<tr>
<td>Protocol</td>
<td>MP pulse therapy for 3 days + randomized VBL vs VP-16</td>
<td>Randomized Pred/VBL vs Pred/VBL/VP-16; continuation: 6-MP/Pred/VBL +/- VP-16</td>
<td>RO+: MTX randomized; 12-wk induction if poor response at 6 wk</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>6 mo</td>
<td>6 mo</td>
<td>6 mo/1 y</td>
</tr>
<tr>
<td>Response rate</td>
<td>53%</td>
<td>67%</td>
<td>RO– 86% RO+ 72%</td>
</tr>
<tr>
<td>Reactivation rate</td>
<td>58%</td>
<td>46%</td>
<td>RO– 54% (6 mo), 37% (12 mo) RO+ 25%</td>
</tr>
<tr>
<td>Highlights</td>
<td>• Weekly VBL for 6 mo similar to VP-16 in outcomes for MS-LCH • Lungs, liver, hematopoietic system, spleen, age &lt;2 y, and poor response at 6 wk identified as risk factors</td>
<td>• Addition of VP-16 in induction does not improve outcome • Addition of VP-16 for RO+ may reduce mortality • Age &lt;2 y without RO+ not a risk factor</td>
<td>MS-LCH RO+: • No benefit of adding methotrexate • Prolonged duration of therapy reduces reactivation MS-LCH RO–: • Prolonged duration of therapy reduces reactivation • Reinduction in poor responders improves response rate</td>
</tr>
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</table>

6-MP, 6-mercaptopurine; LCH, Langerhans cell histiocytosis; mo, months; MP, methylprednisolone; MS-LCH, multisystem LCH; MTX, methotrexate; Pred, prednisone; RO+, risk organ–positive; RO–, risk organ–negative; VBL, vinblastine; VP-16, etoposide; wk, weeks; y, year.

6 to 12 months for patients with single-system disease (craniofacial bones or multifocal bone). Stratum 2 is testing the vincristine/prednisonet/cytarabine-based therapy with randomized maintenance (indomethacin vs 6-mercaptopurine/methotrexate) for patients who have low-risk MS-LCH and treatment failure or reactivation. Stratum 3 is assessing the efficacy of salvage with a cladribine/cytarabine combination in patients with risk organ–positive (RO+) MS-LCH whose disease fails to respond to first-line treatment. Stratum 4 is studying reduced-intensity hematopoietic stem cell transplant as a salvage option for patients who have MS-LCH with risk-organ involvement and who fail stratum 1 and stratum 3 therapies. Stratum 5 is prospectively exploring the effectiveness of cladribine in tumors CNS-LCH and whether intravenous immunoglobulin or cytarabine will affect the progression of ND-LCH of the CNS.

### Single-System LCH

There is no standard of care for the management of patients presenting with single-system disease because these patients were not included in clinical trials. In most cases, isolated LCH skin lesions regress spontaneously and warrant only observation. Infants, however, require close observation because a large proportion of them are likely to progress to high-risk, disseminated disease. Patients who have symptomatic/refractory skin lesions have been treated with topical corticosteroids/tacrolimus, nitrogen mustard, thalidomide (Thalomid, Celgene), psoralen and ultraviolet A (PUVA) therapy, surgical excision, oral corticosteroids, or minimal systemic chemotherapy.

Unifocal bone LCH usually resolves with curettage and/or intralesional corticosteroid injections. Low-dose radiation, although effective, is reserved for emergency situations, such as optic nerve or spinal cord compression. The current standard of care for patients with so-called CNS-risk craniofacial bone lesions and multifocal bone lesions is 12 months of therapy with vinblastine and corticosteroids. Indomethacin and bisphosphonates have also been used effectively in cases of up-front or relapsed multifocal bone LCH.

### Multisystem LCH

#### Low Risk: Risk Organ Not Involved

The standard recommended therapy for low-risk multisystem LCH, which is based on the LCH-III trial findings, is 12 months of therapy with vinblastine/prednisonel; this has reduced the reactivation rate from the historical 50% to 30%. On the basis of the myeloid origin theory of LCH, some investigators have attempted to use cytarabine alone or...
in combination with other agents to treat MS-LCH.\textsuperscript{39,46} Long-term randomized studies, however, are needed to compare these regimens with vinblastine/prednisone in terms of risk for reactivation and late sequelae. The overall survival of patients with low-risk LCH is approximately 100%; however, these patients are at risk for late morbidity related to reactivation and late sequelae such as diabetes insipidus, ND-LCH, and endocrine abnormalities.

**High Risk: Risk Organ Involved.** Therapy for this group of patients, who have an overall survival rate of 84%, is the most challenging. The current standard of care for them consists of treatment with vinblastine and prednisone for 1 year. Previous attempts at adding etoposide, methotrexate, cytarabine, doxorubicin, or cyclophosphamide failed to provide significantly better outcomes.\textsuperscript{36,37,39,47}

**Second-Line Therapy**

Salvage therapy for LCH usually includes agents active against the myeloid cells, such as nucleoside analogues. Most data for salvage therapy come from small case series or retrospective studies (Table 4). Monotherapy with clofarabine and a combination strategy of cladribine plus cytarabine seem to be the most promising; however, these regimens can be quite myelosuppressive and have been associated with a high risk for infections and treatment-related mortality.\textsuperscript{48,49} Allogeneic bone marrow transplant is also an effective option, salvaging 3 of every 4 patients, especially in the modern era of reduced-intensity conditioning regimens with less transplant-related mortality.\textsuperscript{50}

**Targeted Therapies**

With the identification of \textit{BRAF} V600E and other mutations in the MAPK pathway in LCH, early-phase trials were begun to look at targeted therapy in the clinical setting.

**\textit{BRAF} Inhibitors**

Vemurafenib was the first \textit{BRAF} inhibitor to be studied in other \textit{BRAF}-mutant tumors, such as melanoma. Early trials with vemurafenib in adults have shown a durable response in the majority of patients. A case series of 8 adult patients with refractory ECD/LCH highlighted a significant response in all patients at a mean follow-up period of 10 months. A phase 2 clinical trial in adults with \textit{BRAF}-mutant ECD/LCH demonstrated disease regression in 86% patients, with none of the patients progressing while on therapy.\textsuperscript{51,52} A case report demonstrated a significant sustained response to vemurafenib in an infant with high-risk LCH.\textsuperscript{53} A phase 1/2 trial of dabrafenib (Tafinlar, Novartis) in a pediatric population is ongoing, with early patients showing an encouraging response (NCT01677741). Among patients with ND-LCH, 75% responded to vemurafenib, which is promising.\textsuperscript{34}

**MEK inhibitors**

The efficacy of the MEK inhibitors trametinib (Mekinist, Novartis) and cobimetinib (Cotellic, Genentech) was first reported in non-LCH histiocytosis, with sustained responses.\textsuperscript{21} The \textit{MAP2K1} mutation is nonresponsive to trametinib in vivo and in vitro.\textsuperscript{54} An ongoing trial of single-agent cobimetinib in adult patients with histiocytic disorders has shown robust responses.\textsuperscript{55} Interestingly, a patient in whom resistance to dabrafenib developed responded with the addition of trametinib.\textsuperscript{56} This finding led to an ongoing trial with a combination of dabrafenib and trametinib in children. The rationale for combination therapy is to reduce resistance, provide synergistic downstream blockade of the MAPK pathway, and potentially decrease the toxicity profile. In studies of adults who had melanoma, the rates of squamous cell carcinoma and keratoacanthoma were significantly lower in patients

\begin{table}[h]
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\begin{tabular}{|c|c|c|c|c|}
\hline
Regimen & Study & EFS & Survival Rate (N) & Toxicity \\
\hline
2-CdA (5 mg/m\textsuperscript{2} × 5 d) & LCH-S-98 & NR & RO+ 56\% (51) RO− 90\% (25) & Minimal \\
\hline
2-CdA/Ara-C (9 mg/m\textsuperscript{2}; 500 mg/m\textsuperscript{3} BID × 5 d) & LCH-S-2005 & 71\% (1 y) & RO+ 85\% (27) & Universal (2 toxic deaths, 5 ICU) \\
\hline
Clofarabine (25 mg/m\textsuperscript{2}/d × 5 d) & Retrospective & 75\% (1 y) & RO+ 67\% (3) R0− 100\% (8) & Intermediate \\
\hline
\end{tabular}
\caption{Treatment Options for Relapsed/Refractory Langerhans Cell Histiocytosis}
\end{table}

2-CdA, cladribine; Ara-C, cytarabine; BID, twice a day; d, days; EFS, event-free survival; ICU, intensive care unit; NR, not reported; RO, risk organ; y, years.

treated with a combination of MEK and BRAF inhibitors than in those treated with a BRAF inhibitor alone. One hypothesis is that the combination protected against the paradoxical activation of wild-type BRAF.\textsuperscript{57-59}

Although targeted therapies do not cause the conventional toxicities seen with chemotherapy, they do have novel toxicities, some of which are presumably unknown. Vemurafenib was associated with de novo squamous cell carcinoma in nearly half of patients with LCH/ECD who received the drug, which was attributed to the paradoxical activation of wild-type BRAF. Skin irritation was nearly universal; fatigue, arthralgia, hypertension, diarrhea, alopecia, and nausea were other known adverse reactions. In addition, MEK inhibitors have been associated with ocular side effects.\textsuperscript{52,60,61}

The optimal duration of therapy with targeted agents is unknown at present, which makes it difficult to discontinue these drugs in patients showing a response. Preliminary data suggest reactivation rates of up to 75% after the discontinuation of therapy.\textsuperscript{62}

Acquired resistance to BRAF inhibitors is known to occur in adults with melanoma. Although the most common cause of this phenomenon is reactivation of the MAPK pathway through MEK, the further increase in tumor heterogeneity that occurs gives rise to other mechanisms of resistance in metastatic lesions.\textsuperscript{63}

**Future Directions**

The ongoing areas of concern in LCH are the high rate of disease reactivation, the poor outcomes of patients with high-risk disease and a slow early response, and our inadequate understanding of neurodegenerative disease and its optimal therapy. Future research needs to be refined and reshaped to provide the following:

1. A new risk stratification schema that incorporates MAPK mutations;
2. A better understanding of the pathogenesis of CNS neurodegenerative disease;
3. The optimal timing and appropriate use of targeted therapies;
4. Ways to target the tumor microenvironment.

The current frontline therapy for LCH is simple and nonintensive, with minimal therapy-related toxicity. However, could this mild therapy be in part responsible for the high reactivation rates and long-term sequelae of the disease? LCH recurs in nearly 30% of patients within 2 years of the end of therapy, and the recurrence in many cases responds to the same therapy used earlier. The ongoing LCH-IV trial is testing the hypothesis that therapy that is more prolonged (24 vs 12 months) or more intense (with or without 6-mercaptopurine) will be able to reduce the rate of reactivation in patients with RO+ MS-LCH.

Targeted therapy must be viewed not as a replacement but as an additional tool that should be used judiciously. The questions of the optimal timing of targeted therapy (as salvage, up-front, or maintenance therapy) and whether it should be given alone or in combination with chemotherapy need to be explored and answered. Current salvage therapies directed at myeloid cells and stem cell transplant entail a considerable burden of toxicities. Targeted therapy, which could be used as a bridging therapy for poor responders before salvage, might play a significant role in this situation. If a subset of high-risk patients with \textit{BRAF\textsuperscript{V600E}} DNA in their peripheral blood were identified, they might be appropriate candidates for the up-front use of targeted therapy in combination with standard therapy, with the aim of decreasing recurrences and long-term sequelae. Another question worth exploring would be whether the addition of a BRAF/MEK inhibitor in the maintenance phase could decrease recurrences and long-term sequelae.

The revision of risk stratification on the basis of the presence of activating mutations, and the redefinition of hematopoietic and CNS involvement on the basis of the detection of activating mutations in the bone marrow, PBMCs, and cerebrospinal fluid, must be considered. Recent insights into the pathogenesis of ND-LCH may suggest an active disease process, challenging the paraneoplastic theory. This, coupled with the clinical response to BRAF inhibitors, would make a case for using targeted therapy in patients at high risk for neurodegeneration.\textsuperscript{34}

The tumor microenvironment plays an important role in LCH tumorigenesis. The histologic milieu, cytokine studies, and clinical observations suggest that an intense local and systemic inflammatory response could be one of the factors leading to long-term damage, morbidity, and mortality.\textsuperscript{64-68} Targeting the inflammatory cascade would provide an attractive multipronged approach to disrupting the tumor microenvironment. Clinical experience with bisphosphonates, etanercept (Enbrel, Amgen/Pfizer), and indomethacin provides the rationale for targeting the inflammation generated by the pathologic cells in LCH.\textsuperscript{69-72} The expansion of regulatory \(T\) cells in LCH causes us to speculate that targeting T-reg, or overcoming tolerance, might be beneficial.\textsuperscript{73} Interestingly, a recent immunohistochemical study demonstrated significant expression of the programmed death 1 (PD-1) ligand in a number of histiocytic disorders, including LCH.\textsuperscript{74} These results need to be confirmed in large studies, but they suggest that the use of checkpoint inhibitors for patients with refractory or relapsed disease might be a subject worthy of future study.
Disclosures

Dr. Thacker and Abla have no relevant disclosures.

References