


A Consensus Review on Malignancy-Associated Hemophagocytic Lymphohistiocytosis in Adults

Naval Daver, MD ¹; Kenneth McClain, MD, PhD²; Carl E. Allen, MD, PhD²; Sameer A. Parikh, MD³; Zaher Otrrock, MD⁴; Cristhiam Rojas-Hernandez, MD⁵; Boris Blechacz, MD, PhD⁶; Sa Wang, MD⁷; Milen Minkov, MD⁸; Michael B. Jordan, MD⁹; Paul La Rosée, MD¹⁰; and Hagop M. Kantarjian, MD¹

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of severe immune activation and dysregulation resulting in extreme and often life-threatening inflammation. HLH has been well recognized in pediatric populations, and most current diagnostic and therapeutic guidelines are based on pediatric HLH. Recently there has been recognition of HLH in adults, especially secondary to immune deregulation by an underlying rheumatologic, infectious, or malignant condition. This review is focused on malignancy-associated HLH (M-HLH), in which possible mechanisms of pathogenesis include severe inflammation, persistent antigen stimulation by the tumor cells, and loss of immune homeostasis because of chemotherapy, hematopoietic stem cell transplantation, or infection. Previously considered rare, M-HLH may occur in up to 1% of patients with hematologic malignancies. M-HLH is often missed or diagnosed late in most published studies, and it has been associated with a poor median survival of less than 2 months. Identification of the clinical and laboratory features specific to M-HLH in adults may allow early detection, consultation with HLH experts, and intervention. Improved management of adult M-HLH with optimal combinations of T-lympholytic and immunosuppressive agents and the incorporation of novel agents based on the pediatric experience hopefully will improve outcomes in adults with M-HLH. *Cancer* 2017;123:3229-40. © 2017 American Cancer Society.

KEYWORDS: adults, hemophagocytosis, lymphohistiocytosis, malignancy.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of severe immune activation and deregulation characterized by hyperactive macrophages and lymphocytes, proinflammatory cytokine hypersecretion, tissue infiltration, hemophagocytosis, and organ damage.^{1,2} An excessive deregulated inflammatory response plays a central role in the pathogenesis of HLH, including: 1) hyperactivation of CD8-positive T lymphocytes and macrophages, 2) proliferation and infiltration of these inflammatory cells in organs, and 3) uncontrolled production of type 1 T-helper cell cytokines. Severe and often life-threatening inflammation and immune-mediated organ damage are the clinical hallmarks of HLH.^{1,3,4} HLH occurs either as primary HLH, characterized by genetic defects in cytotoxic immune function, or as secondary or as acquired HLH, characterized by reactive immune overstimulation to an aberrant nonself-antigen.⁵⁻⁷ “Secondary” HLH may also have “primary” cofactors, as demonstrated by so-called hypomorphic mutations in HLH-associated gene loci.⁸

Historically, most diagnostic guidelines, international databases, and treatment trials in HLH have focused on pediatric populations. However, HLH is not a pediatric-specific disease and may occur at any age. A nationwide survey in 300 Japanese hospitals noted that 40% of HLH cases occurred in adults.⁹ HLH in adults is frequently secondary to an underlying stimulus and has been associated with dismal outcomes. Data regarding HLH in the setting of malignancy in adults are very limited. Recent retrospective studies have demonstrated that this entity may occur in up to 1% of patients with underlying malignancies at diagnosis, during therapy, or even after control of the underlying malignancy, and it may be more common than previously estimated.¹⁰ The current review was conceptualized and formulated by a group of experts in adult and pediatric HLH to update the current knowledge of malignancy-associated HLH (M-HLH) with a focus on

Corresponding author: Naval Daver, MD, Department of Leukemia, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 0425, Houston, TX 77030; ndaver@mdanderson.org

¹Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas; ²Histiocytosis Program, Texas Children’s Cancer Center, Texas Children’s Hospital, Houston, Texas; ³Division of Hematology, Mayo Clinic, Rochester, Minnesota; ⁴Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri; ⁵Section of Benign Hematology, The University of Texas MD Anderson Cancer Center, Houston, Texas; ⁶Department of Gastroenterology, Hepatology, and Nutrition, The University of Texas MD Anderson Cancer Center, Houston, Texas; ⁷Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, Texas; ⁸University Clinic of Pediatrics, St. Anna Children’s Hospital, Medical University of Vienna, Vienna, Austria; ⁹Langerhans Cell Histiocytosis Center, Cincinnati Children’s Hospital, Cincinnati, Ohio; ¹⁰Department of Internal Medicine, Schwarzwald-Baar Clinic, Villingen-Schwenningen, Germany

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clinical aspects that would help academic and community hematology-oncology specialists consider, diagnose, and manage this entity.

PRIMARY (GENETIC) AND SECONDARY (REACTIVE) HLH

Primary HLH (also called familial or genetic HLH) is an autosomal recessive disease with an incidence of from 1 in 50,000 to 1 in 100,000 live-born children.^{11,12} Patients often have a clear familial inheritance or an identifiable genetic mutation. These are most frequently biallelic mutations in genes encoding for perforin, syntaxin 11, mammalian uncoordinated 18-2 homolog (Munc-18-2), Munc-13-4, and other proteins involved in cytotoxic granule activation, polarization, priming, fusion, or function.^{1,13} In many circumstances, no clear immune trigger is identifiable.¹⁴ Primary HLH carries a high morbidity and mortality and is associated with a median survival of less than 2 months without treatment.^{15,16} The development of effective treatment protocols and a concerted international effort have significantly improved the recognition and long-term survival (>50%) in patients with primary HLH.¹⁷ Primary HLH has traditionally been considered a disease of pediatric populations. Of note, systematic genetic evaluation in adolescent and adult patients with HLH identified hypomorphic mutations (*PRF1*, *MUNC13-4*, *STXBP2*, *STX11*, *SH2D1A*, *BIRCA4*) in 7% to 14% of patients, suggesting that late-onset primary HLH occurs more commonly than previously suspected.^{8,18}

Secondary HLH includes adults and older children who lack a family history or a known genetic cause for HLH. The list of triggers associated with secondary HLH is extensive.¹⁹ Secondary HLH is the more frequent presentation of HLH in adults²⁰ and comprises 2 main groups: M-HLH and nonmalignancy-associated HLH. Frequently noted malignancy triggers for adult M-HLH include hematologic malignancies, such as lymphomas, T-cell/natural killer (NK)-cell disorders, acute leukemias, lymphoproliferative diseases, and myelodysplastic syndrome.^{10,21-33} Nonmalignancy-associated, secondary HLH is further subclassified as infection-related HLH (especially virally induced by Epstein-Barr virus, cytomegalovirus, or human immunodeficiency virus, but also induced bacterial, protozoal, or mycotic infection),³⁴⁻³⁸ autoimmune disease-related HLH (usually classified as macrophage activation syndrome [MAS] and most commonly triggered by systemic lupus erythematosus, systemic juvenile idiopathic arthritis, polymyositis, and vasculitis),^{37,39,40} spontaneous or iatrogenic immune suppression-related HLH, and post-hematopoietic or solid organ transplantation HLH.^{41,42}

Secondary HLH in adults frequently manifests as an aggressive disease, with mortality rates ranging from 8% in MAS complicating systemic juvenile idiopathic arthritis⁴³ to > 80% in M-HLH.^{32,33}

It is also important to note that secondary HLH in adults is often multifactorial, with more than 1 etiology contributing to the immune dysregulation. In either case, efforts should be made to promptly identify the underlying trigger and expediently initiate therapy if the diagnosis of HLH is suspected, regardless of the classification.

PHYSIOLOGY OF HLH

Patients with HLH have deregulation of the immune system, including predisposing immunodeficiency, immune activation, and immune activation-mediated organ damage.^{1,44} Jordan et al used perforin-deficient mouse models to gain insight into the pathophysiology of primary HLH.⁴⁴ Perforin-deficient mice did not spontaneously develop HLH. However, upon exposure to lymphocytic choriomeningitis virus, they manifested all of the clinical features of HLH, including fever, splenomegaly, pancytopenia, hypertriglyceridemia, hypofibrinogenemia, elevation of multiple serum cytokine levels, and histologic evidence of hemophagocytosis in many tissues (Fig. 1). Those investigators demonstrated that, in murine models, CD8-positive T cells, but not NK cells, played a central role in the evolution of HLH. Cytokine-neutralization studies revealed that interferon- γ (IFN- γ) was uniquely essential and was produced as a result of increased antigen presentation to CD8-positive T cells.

Another recently published study investigated the homeostasis of regulatory T (Treg) cells and CD8-positive T cells in perforin knockout and wild-type mice during lymphocytic choriomeningitis virus-mediated inflammation. The perforin knockout mice had disease that clinically resembled HLH. T-cell interrogation in these mice demonstrated a major reduction of the Treg compartment in the spleen and lymph nodes and 2-fold decreased expression of the activation marker CD25 on the Treg cell surface. Conversely, CD8-positive T cells exhibited greater expression (14-fold) of CD25 and other T-cell activation markers, such as CD69. The serum-soluble CD25 (soluble interleukin-2 α [s-IL2 α]) in the perforin-deficient mice was also significantly higher. These data suggest that HLH is a disorder of Treg-CD8-positive balance and IL-2 network homeostasis, in which CD8-positive T cells are excessively activated and successfully outcompete Treg cells for IL-2 with resultant Treg hypofunction.⁴⁵

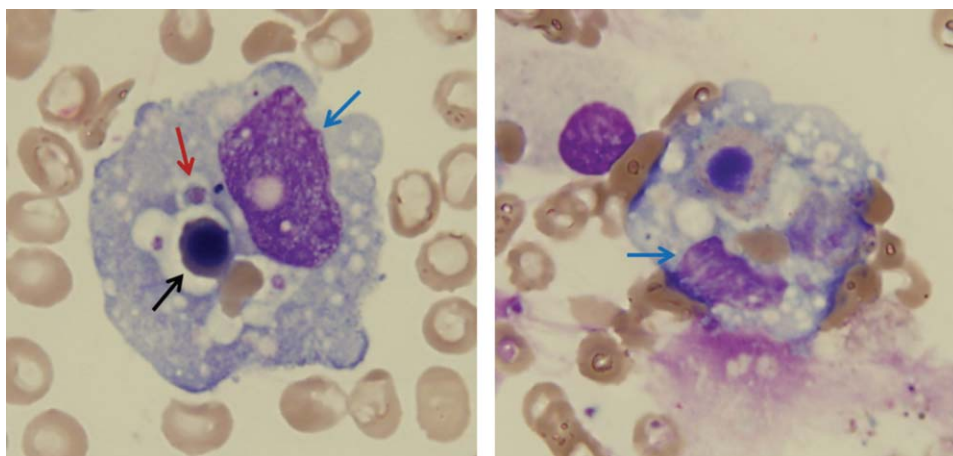


Figure 1. Morphologic features of hemophagocytosis are observed on a bone marrow aspirate smear (Wright-Giemsa stain, original magnification $\times 500$). Blue arrows indicate white blood cells; black arrow, a nucleated erythrocyte; red arrow, a platelet.

Similar to primary HLH, immune-activation and immune-mediated pathology likely play a central role in the evolution of secondary HLH.¹ Biopsies of lymphoid tissues or histologic examination of liver tissue from patients with secondary HLH reveal highly activated macrophages and lymphocytes. Secondary HLH is characterized by acute clinical signs and symptoms of immune activation, including hepatomegaly, jaundice, adenopathy, rash, seizures, and focal neurologic deficits, as well as laboratory measures, such as very high serum levels of numerous cytokines, including IFN- γ , tumor necrosis factor- α , IL-6, IL-10, and macrophage-colony-stimulating factor.^{46,47} Among these, IFN- γ appears to be 1 of the most sensitive and early indicators of disease activity. High IFN- γ levels correlated positively with high peripheral leukocyte count and high serum lactate dehydrogenase and negatively with the CD4/CD8 T-cell ratio.⁴⁷ Furthermore, IFN- γ , but not tumor necrosis factor, was detected just before a relapse marked by spiking fever. Zhang et al noted clinical features consistent with HLH/MAS in patients with systemic juvenile idiopathic arthritis who were identified as heterozygous for rare variants of primary HLH-associated genes.¹³ These results suggest that the inflammatory stress of the rheumatologic condition unmasked HLH in these predisposed individuals.

PATHOLOGY AND THE ROLE OF HEMOPHAGOCYTOSIS IN M-HLH

In primary HLH, a finding of hemophagocytosis or lymphohistiocytosis on tissue evaluation is supportive but, on its own, lacks sensitivity and specificity to diagnose secondary HLH, as previously described,^{48,49} including

adult M-HLH. In a large series of 162 patients with HLH, hemophagocytosis was observed in approximately 70% of patients who had a confirmed diagnosis of HLH; however, it was also observed in approximately 40% patients who had a similar clinical presentation but did not meet other criteria for HLH and were not considered to have a clinical diagnosis of HLH.⁵⁰ These data suggest that the presence or absence of phagocytes should be considered as 1 supportive feature to be evaluated along with other clinical and laboratory manifestations during the workup of M-HLH.

A bone marrow biopsy is frequently performed as a part of the initial workup in patients with hematologic malignancies (acute or chronic leukemia, lymphoma, myeloma). Hemophagocytosis often is not identified on the initial bone marrow biopsy, because pathologic alterations caused by HLH may take days or a week to become manifest.⁴⁹ The absence of hemophagocytosis on the initial bone marrow biopsy should not delay therapy in patients with an otherwise high suspicion for hemophagocytosis. Initial bone marrow biopsies in more fulminant cases of HLH or follow-up bone marrow evaluations in a patient with HLH may reveal increased small lymphocytes, predominantly T cells; as well as histiocyte infiltrate. The histiocytes are composed predominantly of mature macrophages, which often have engulfed red blood cells, nucleated red blood cells, or neutrophils. In addition to bone marrow evaluations, changes consistent with HLH may be observed in liver, lymph node, or splenic tissue. In liver biopsy specimens, hemophagocytosis, when apparent, typically manifests as perivascular and portal lymphohistiocytic infiltrates. Lymph nodes exhibit a preserved lymph node architecture, with a sinusoidal

infiltration of bland histiocytes containing red blood cells admixed with occasional lymphocytes and neutrophils. Splenectomy is rarely performed but, when available in a patient with HLH, splenic tissue often reveals increased macrophages, including phagocytes, in the red pulps.

CD163 functions well in paraffin-embedded tissue specimens (bone marrow, lymph node, liver tissue) to highlight increased macrophages and is frequently used in the workup of tissue specimens from patients suspected to have HLH.⁵¹ In addition to macrophages, increased megakaryocytes and erythroid hyperplasia as a result of compensatory hematopoiesis may be noted. Mild reticulin fibrosis and dysplastic changes in red blood cells and granulocytes have also been described as tissue manifestations of HLH. In patients with a high clinical suspicion of HLH or otherwise confirmed HLH, available tissue could be used to identify potential triggers for M-HLH, such as T-cell/NK-cell neoplasm, B-cell lymphoproliferative disease, early myelodysplastic syndrome, or aplastic anemia, through pathologic evaluation by an experienced hematopathologist, directed flow cytometry, T-cell receptor clonality, and immunohistochemistry stains or for infectious triggers by performing Epstein-Barr encoding region in situ hybridization, cytomegalovirus and herpes simplex virus immunohistochemistry, and viral polymerase chain reaction analyses.

SECONDARY M-HLH

Most malignancies that trigger secondary HLH in children and adults are hematologic malignancies, including lymphomas and leukemia. M-HLH is diagnosed more frequently in adults.²⁰ Machaczka et al noted that the prevalence of M-HLH was 0.9% in adults with hematologic cancers but could be as high as 20% in those with specific, rare types of B-cell lymphomas (intravascular B-cell lymphoma or B-cell lymphoma without peripheral adenopathies) and T-cell lymphomas (nasal NK-cell or panniculitis-like subtypes).¹⁰

PATHOPHYSIOLOGY OF M-HLH

M-HLH may manifest during the treatment of a known malignancy or as the presenting feature of an as yet undiagnosed malignancy. Several possible mechanisms of pathogenesis have been identified. First, it is postulated that the hyperinflammation is triggered by the neoplasm because of an excessive secretion of proinflammatory cytokines and persistent antigen stimulation by the tumor cells. Second, inherited immune disorders that predispose to both HLH and malignancy (eg, X-linked lymphoproliferative diseases) may further predispose patients to the

development of M-HLH. Third, M-HLH may also occur during chemotherapy. The combined immunodeficiency generated by the underlying malignancy and the loss of immune homeostasis because of chemotherapy (or hematopoietic stem cell transplantation or infection) further aggravates T-cell dysfunction that lowers the threshold for triggering HLH in these patients. Fourth, malignancy-induced immunodeficiency combined with tumor-directed therapy predisposes to infections, which may act as independent triggers of M-HLH in these patients.⁵² Delavigne et al identified M-HLH in 32 patients with acute myeloid leukemia who were receiving induction therapy. A potential infectious trigger for HLH was identified in 24 patients (75%) and included a mixture of bacterial, viral, and fungal infections, highlighting the importance of proactively evaluating for infectious etiologies in adult patients with suspected M-HLH.³¹

More recently, symptoms similar to those observed in HLH have been described in patients who were receiving immunotherapies. These symptoms are caused by proinflammatory cytokine overproduction by T-cell-activating immunotherapies used in the treatment of leukemia/lymphoma and solid tumors (eg, bispecific monoclonal antibody blinatumomab, chimeric antigen receptor T-cell therapies, dendritic vaccines, combinations with checkpoint inhibitors, and immunomodulatory drugs, such as lenalidomide and thalidomide).^{4,24,25,53} The cytokine release syndrome with these agents bears a clinical and immunologic signature similar to that of HLH and often responds to the therapies used in HLH.^{54,55}

CLINICAL COURSE OF M-HLH

The clinical course of M-HLH often rapidly progresses and is characterized by poor outcomes (Table 1).^{10,23-25,32,33} Lehmborg et al identified M-HLH in 21 pediatric and adolescent patients, most of whom had T-cell (n = 12) or B-cell (n = 7) neoplasms, with Epstein-Barr virus as a co-trigger in 5 patients. An additional 8 patients had chemotherapy-induced HLH. The median survival of patients with M-HLH was 1.2 months.²⁵ Machaczka et al noted that 8 of 887 (0.9%) patients diagnosed with hematologic malignancies developed M-HLH.¹⁰ Six of those 8 patients received HLH-directed therapy, and 3 achieved remission. The median overall survival was 2.4 months, and only 1 remission was durable. Shabbir et al identified 18 adults who had HLH diagnosed at 1 institution, of whom 6 had M-HLH (4 patients with an underlying hematologic malignancy, 2 patients postautologous stem cell transplantation). Corticosteroids and/or cyclosporine were used most frequently to treat patients.²⁴ Other

TABLE 1. Summary of Malignancy-Associated Hemophagocytic Lymphohistiocytosis Clinical Outcomes Across Different Institutions

Study	No. of Patients	Most Frequent Associated Malignancy	Six-Month Survival Rate, %	Median Survival, mo
Tamamyam 2016 ³³	35	AML/MDS (n = 13), T-cell lymphoma (n = 10), DLBCL (n = 6), HL (n = 6), CLL (n = 4), CML (n = 2), follicular lymphoma (n = 2)	30	2.0
Parikh 2014 ²³	32	T-cell lymphoma (n = 19), DLBCL (n = 6), EBV-associated PTLD (n = 3), HL (n = 1), CMML (n = 1), hemangioendothelioma (n = 1), systemic histiocytosis (n = 1)	Not reported	1.4
Otrock & Eby 2015 ³²	21	B-cell neoplasms (n = 10), T-cell neoplasms (n = 6), HL (n = 3), AML (n = 1), MDS (n = 1)	20	1.1
Lehmberg 2015 ²⁵	21	T-cell neoplasms (n = 12), B-cell neoplasms (n = 7)	67	1.2
Machaczka 2011 ¹⁰	8	HL (n = 2), MM (n = 2), 1 each of B-CLL, PTCL, AILD, WM, ATL	38	2.4
Shabbir 2011 ²⁴	6	AML (n = 2), T-cell lymphoma (n = 2), postauto-SCT for MM (n = 2)	Not reported	1.2 (Entire adult HLH cohort; n = 18)

Abbreviations: AILD, angioimmunoblastic lymphadenopathy; AML, acute myeloid leukemia; ATL, adult T-cell leukemia; B-CLL, B-cell chronic lymphocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; HL, Hodgkin lymphoma; HLH, hemophagocytic lymphohistiocytosis; MDS, myelodysplastic syndrome; MM, multiple myeloma; PTCL, peripheral T-cell lymphoma; PTLD, post-transplantation lymphoproliferative disorder; SCT, stem cell transplantation; WM, Waldenström macroglobulinemia.

agents used included etoposide, intravenous immunoglobulin, cyclophosphamide, and chemotherapy, indicating heterogeneous treatment approaches to M-HLH. The 6-month mortality rate in that study was 72%, and the median survival was 1.2 months. Parikh et al reviewed patients who were treated at the Mayo Clinic over a 15-year period (1996-2011) and noted that, among 250 adults in whom a diagnosis of HLH was suspected, 62 met the HLH-2004 diagnostic criteria²³ and were included in the final analysis. Thirty-two of those 62 patients (52%) had M-HLH. The median survival of the entire cohort was 2.1 months, and the median survival of patients with M-HLH was 1.4 months compared with 22.8 months for adults who had nonmalignancy-associated HLH. On multivariate analysis, the presence of malignant tumor and hypoalbuminemia were significant predictors of inferior survival. In another study on the management of adult HLH, Otrock and Eby reported that 29% (21 of 73) of the adults who had HLH at their institution had malignancy-associated disease. Adult patients with M-HLH had worse survival compared with those who had nonmalignancy-associated HLH (median overall survival, 1.13 vs 46.53 months, respectively; $P < .0001$).³²

Tamamyam et al retrospectively identified pathologic hemophagocytosis and/or lymphohistiocytosis in 61 adults with underlying malignancies who were treated between 1991 and 2001 at The University of Texas MD Anderson Cancer Center.³³ Thirteen of 61 patients (21%) in that study met the HLH-2004 diagnostic criteria. To identify potentially missed cases of HLH, the authors reviewed the published literature and selected additional variables known to be associated with adult

HLH, resulting in an extended diagnostic criteria list of 18 variables. Thirty-five patients had additional systemic variables that were consistent with HLH. The median survival was 2 months among patients who received HLH-directed therapy and 2 months among those who did not receive HLH-directed therapies. Seventeen of 33 patients (52%) died within 8 weeks after diagnosis, and 23 (70%) died within 6 months after diagnosis.³³

DIAGNOSIS OF M-HLH

Traditional Diagnostic Criteria

The initial HLH guidelines in 1991 included 5 features: 1) fever, 2) splenomegaly, 3) cytopenias affecting at least 2 or 3 lineages in the peripheral blood, 4) hypertriglyceridemia and/or hypofibrinogenemia, and 5) hemophagocytosis in bone marrow, spleen, or lymph nodes.⁵⁶ The 2004 guidelines included 3 additional criteria: 6) low or absent NK-cell activity, 7) hyperferritinemia, and 8) high levels of s-IL2 α . Five of 8 criteria must be fulfilled to make a diagnosis of secondary HLH.^{2,19,56} However, patients with a molecular diagnosis of HLH do not need to fulfill the diagnostic criteria to diagnose primary HLH in the appropriate clinical scenario. It is important to note that the pathologic finding of hemophagocytosis is not pathognomonic for HLH, which is a common cause for missed or delayed diagnosis among treating physicians.

It is important to note that the 1991 and 2004 guidelines were developed using pediatric populations. Information and diagnostic guidelines specific to adult HLH are limited, and current diagnostic and treatment approaches of HLH in adults are extrapolations from retrospective databases and clinical trials in childhood HLH. These knowledge gaps have led to under-diagnosis or

delayed diagnosis of M-HLH and nonmalignancy-associated HLH in adults, further worsening their outcomes.^{23,32,57} Recent efforts focused on developing adult-specific and malignancy-specific HLH consensus recommendations are underway to improve our ability to rapidly identify and manage this entity.³⁰

Need for Adult M-HLH Diagnostic Criteria

The first critical step in successful treatment of M-HLH is considering the diagnosis. A greater awareness of M-HLH among oncologists and a growing incidence of the entity, especially in wake of the increased use of immune activating and modulating agents, will lead more hematologists and oncologists to consider and initiate a workup for HLH in adults. Unfortunately, currently, there remains significant uncertainty regarding the best approach to diagnose M-HLH in adults.^{4,23,58} The HLH-2004 criteria require 5 of 8 criteria to be met, including 2 criteria (s-IL2r α and NK-cell activity) that typically require send-out specialty laboratory tests and are difficult to obtain in a timely manner in smaller institutions or community hospitals. These tests require from 5 to 8 days to be finalized, even in larger institutions. Nonavailability or delayed availability of these tests may delay confirmation of the diagnosis or referral of adults with HLH to tertiary care facilities. This may further worsen poor outcomes in adult HLH and M-HLH.

The above constraints serve as the impetus to identify and include additional diagnostic variables easily obtained by physical examination and local routine laboratory tests to allow for more rapid suspicion and referral of patients with possible adult M-HLH to specialized centers until prospectively validated, definitive adult M-HLH criteria are developed and validated. We recently proposed 1 such schema for adult M-HLH that incorporated more rapidly and broadly available physical examination and laboratory variables, thereby allowing for possible earlier consideration and referral to tertiary centers for the workup and treatment of adult M-HLH,³³ especially from smaller community institutions. We reviewed the published literature and expert opinions and identified 18 variables closely associated with HLH in peer-reviewed articles. Sensitivity analysis suggested that patients who meet any 5 of these 18 criteria could be considered to have a high likelihood of M-HLH (Fig. 2). We then used the panel of 18 variables to identify patients who would have been diagnosed with HLH using these extended criteria from among the 61 patients who had a known pathologic finding of hemophagocytosis or lymphohistiocytosis from a pathology database for the years

2001 through 2014 at our institution. Thirty-five of the 61 patients (57%) who manifested 5 or more additional findings from our proposed extended criteria, beyond pathologic hemophagocytosis or lymphohistiocytosis, were more likely based on our criteria to have had a systemic M-HLH rather than just a reactive hemophagocytosis or lymphohistiocytosis in the presence of a malignancy. It is noteworthy that 13 of these 35 patients (38%) also met standard HLH-2004 criteria, but the other 22 did not. There was no significant difference in overall survival among the 13 patients who met standard HLH-2004 criteria (median overall survival, 1.43 months) and the 22 patients who did not meet standard HLH-2004 criteria but met our proposed extended 18-point HLH criteria (median overall survival, 1.76; $P = .34$). The 26 remaining patients of the 61 (43%) who had hemophagocytosis or lymphohistiocytosis identified on pathology but met neither standard HLH-2004 criteria nor our extended 18-point HLH criteria had a significantly improved overall survival (median, 17.2 months; $P < .05$). The inferior survival of patients who met standard HLH-2004 criteria or our extended 18-point HLH criteria, but not those who had pathologic evidence of hemophagocytosis/lymphocytosis but met neither criteria, suggests that both criteria may reasonably identify patients who likely have a more aggressive, systemic process requiring directed therapy. It must be noted that our extended 18-point criteria were developed using retrospective data, and it is quite possible that several patients who met our criteria would have met the HLH-2004 criteria if HLH-specific laboratory tests, such as triglycerides, s-IL2r levels, and NK-cell activity, were performed, but these were not done in several patients. The intent of our analysis was not to replace existing HLH standard criteria but rather to highlight that the inclusion of additional diagnostic variables, especially variables that are easily and quickly assessed by routine laboratory or physical examination, may promote early suspicion and workup for HLH in community centers.

These criteria are being prospectively evaluated and compared with standard HLH-2004 criteria in our ongoing clinical trial for M-HLH (clinicaltrials.gov identifier NCT02385110). Ideally, these efforts would need to be conducted on a multicenter, international scale involving patients with suspected M-HLH to efficiently generate reproducible, clinically applicable data. In the interim, a conservative approach is suggested, and a diagnosis and workup of M-HLH should be considered in adult patients with malignancy who have hemophagocytosis in the bone marrow or tissue with unexplained fever under broad

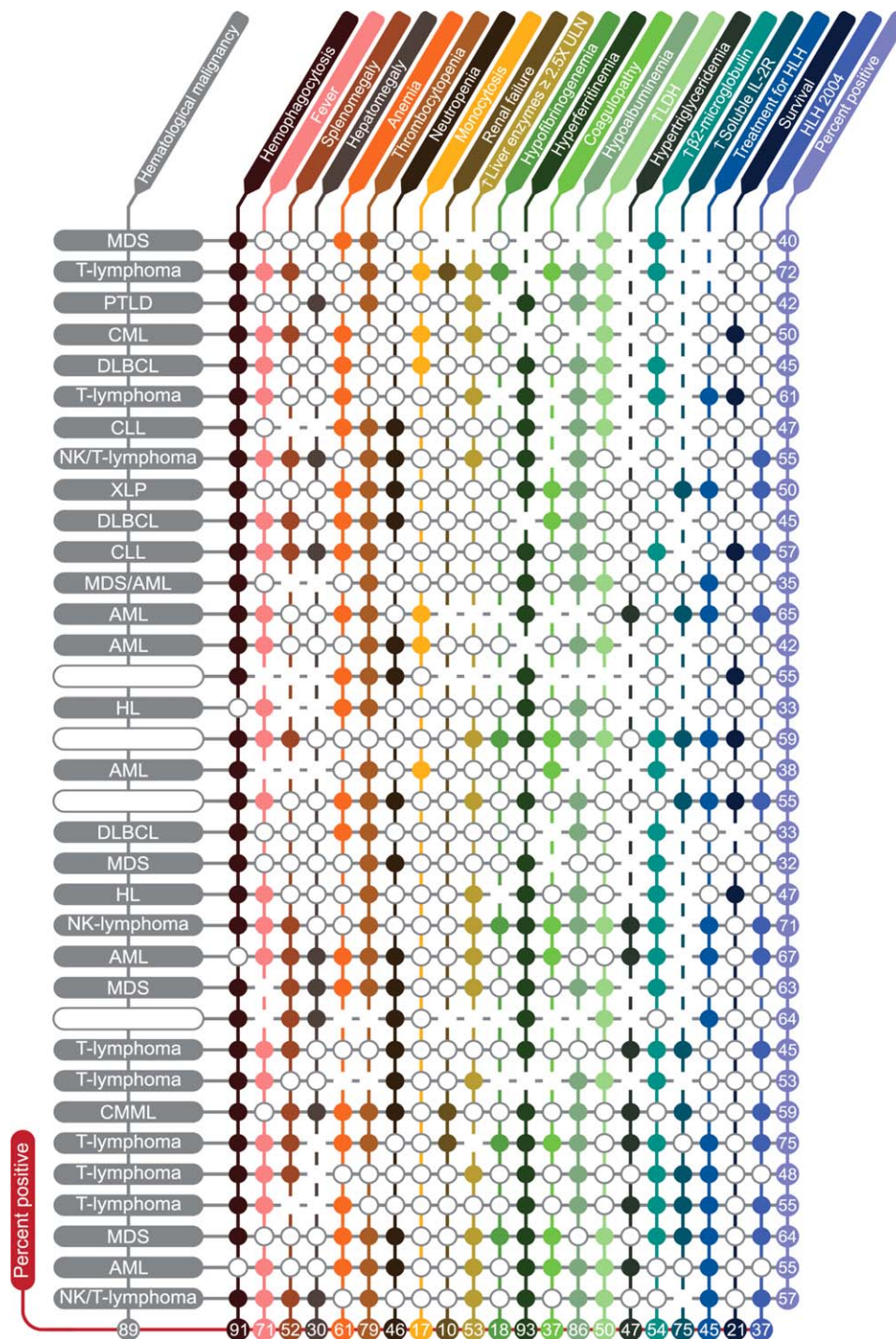


Figure 2. Adult hemophagocytic histiocytosis characteristics and diagnostic variables are illustrated. Each closed circle (●) represents a positive result. Blanks represent missing information. Each row is 1 patient, and each column is a variable. Numbers are the percentages of positive patients (for each characteristic) or the percentage of positive characteristics (for each patient), excluding missing information. The variables evaluated (listed in the order of columns) include bone marrow/lymph node/spleen hemophagocytosis according to pathology evaluation; fever; splenomegaly (clinically palpable spleen); hepatomegaly (clinically palpable liver); anemia (hemoglobin < 9.0 g/L); thrombocytopenia (platelets < $100 \times 10^9/L$); neutropenia (absolute neutrophil count < $1.0 \times 10^9/L$); monocytosis (absolute monocyte count > $1.0 \times 10^9/L$); renal failure ($\geq 50\%$ increase in creatinine over baseline); elevated (\uparrow) hepatic enzymes (≥ 2.5 times the upper limit of normal [ULN]); hypofibrinogenemia (fibrinogen ≤ 150 mg/dL); hyperferritinemia (ferritin ≥ 500 mg/L); coagulopathy (prothrombin time ≥ 1.5 times ULN, and/or partial thromboplastin time ≥ 1.5 times ULN, and/or D-dimer ≥ 10.0 $\mu\text{g}/\text{mL}$); hypoalbuminemia (< 3.5 g/dL); elevated lactate dehydrogenase (LDH) (≥ 2.5 times ULN); hypertriglyceridemia (≥ 265 mg/dL); elevated $\beta 2$ microglobulin (≥ 2 mg/L); and elevated (\uparrow) soluble interleukin-2 receptor (IL-2R [CD25]; ≥ 2400 U/mL). AML indicates acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; HLH 2004, hemophagocytic lymphohistiocytosis 2004 diagnostic criteria; MDS, myelodysplastic syndromes; NK-lymphoma, natural killer cell lymphoma; PTLD, post-transplantation lymphoproliferative disorder; T-lymphoma, T-cell lymphoma; XLP, X-linked lymphoproliferative disease.

antimicrobial treatment, and/or a sudden increase in serum ferritin, and/or unexpected nontumor progression-associated pancytopenia.

THERAPY FOR M-HLH

Traditional HLH Therapy

In addition to the limited awareness and lack of specific diagnostic criteria in adult M-HLH, a third major hurdle to the successful management of M-HLH in adults is the development and validation of an effective multidisciplinary treatment strategy. Furthermore, adult HLH is not a homogeneous disease, and therapy must be tailored to the underlying trigger, performance status of the patient, organ functions, and concomitant therapies.⁵⁹ This is even more critical in the management of M-HLH, in which patients are already functionally and immunologically compromised by the underlying malignancy and chemotherapy.

Traditionally, the initial goal of therapy in HLH has been to suppress the overactive immune system, thus preventing immune-mediated organ damage. Induction therapy is often followed by allogeneic stem cell transplantation in most patients with primary HLH if a suitable donor is available^{1,2} (level of evidence, IIB). The pediatric HLH-94 protocol included an 8-week regimen with etoposide, dexamethasone, and intrathecal methotrexate⁶⁰ (level of evidence, IIA). Etoposide is received at a dose of 150 mg/m² initially twice a week and then weekly, dexamethasone is received orally or intravenously starting at 20 mg/m²/day and is tapered every subsequent week, and children who have evidence of central nervous system involvement receive weekly intrathecal methotrexate and hydrocortisone. This systematic therapeutic approach has improved the outcomes and survival of patients with pediatric (predominantly genetic) HLH. The HLH-2004 protocol (modified from HLH-94) starts cyclosporine at the beginning of induction and adds hydrocortisone to the intrathecal therapy (level of evidence, IIA). The HLH-2004 protocol has completed accrual, and study publication is pending.

Another therapeutic approach has been geared to suppress macrophages and CD8 T lymphocytes with antithymocyte globulin (ATG) in combination with steroids, cyclosporine A, and intrathecal chemotherapy⁶¹ (level of evidence, IIA). Under this treatment protocol, newborns or toddlers receive ATG at a total dosage of 50 mg/kg or 25 mg/kg (this varies according to the severity of disease over the course of 5 days). Methylprednisolone 4 mg/kg daily is administered with ATG for 5 days

and then tapered. Intrathecal methotrexate and corticosteroids are given at various dosages determined by patient age and at various intervals according to the severity of central nervous system involvement. Cyclosporine is added to reach a plasma concentration of 150 ng/mL before hematopoietic stem cell transplantation. Mahlaoui et al evaluated this regimen in 38 consecutive children and reported encouraging response rates (complete response, 73%; partial response, 24%; no response, 1 patient).⁶² Sixteen of 19 responding patients who underwent allogeneic stem cell transplantation early after response were cured, and 60% of patients achieved long-term survival. To improve the existing HLH regimens, a phase 2 multicenter trial that combines elements of both standard induction regimens discussed for HLH, including ATG, etoposide, and dexamethasone in newly diagnosed patients up to age 18 years with HLH, was recently completed, and the results are awaited (clinicaltrials.gov identifier NCT01104025).

Need for Adult M-HLH-Specific Therapeutic Approaches

With greater awareness and targeted laboratory evaluations, many patients who would have been diagnosed with other conditions, such as hepatic or renal failure of unknown etiology, sudden-onset multiorgan failure, culture-negative sepsis, or encephalopathy of unknown etiology, may now have HLH identified. At our centers, we have identified HLH in numerous such patients, including those receiving frontline and salvage therapy for underlying hematologic malignancies. The mortality among patients manifesting M-HLH has been high (median survival, < 2.0 months). A recent analysis from our center indicated that < 50% of adults with M-HLH received HLH-directed therapy because of lack of awareness and missed diagnosis of this condition in adult patients with malignancies. This may be caused by several factors. First, limited awareness and recognition may result in consultation or presentation of patients with M-HLH at an advanced stage with irreversible multiorgan failure in an intensive care setting, when it is no longer feasible to initiate lympholytic or cytotoxic therapy for HLH. Second, patients with M-HLH are already myelosuppressed and immunocompromised, and the addition of further cytotoxic therapy with etoposide or ATG-based regimens carries additional risks and a high mortality. Third, it is debated whether focus should be on therapy of the underlying malignancy or the pathologic inflammation. Although treatment of the underlying disorder intuitively appears to be the correct approach, we have

frequently noted a very aggressive and rapid progression of HLH among our patients with M-HLH, and a majority die from HLH within 2 to 4 weeks despite continued treatment of the underlying malignancy. We believe that the secondary but uncontrolled inflammation, as well as the underlying malignancy, must be addressed, often in a sequential manner. In some patients, it may be possible to address both entities simultaneously; and, if possible, this would be ideal.

Frequently, HLH induces cytokine-dependent cytopenias, HLH-dependent cholestatic icterus, pulmonary infiltrates, encephalopathy, or renal failure, which do not allow the initiation of malignancy-directed (immuno)-chemotherapy. As soon as it is recognized that the organ damage is HLH-triggered, the application of lympholytic agents must be considered despite formal contraindications. In those conditions, we suggest a 2-step approach (level of evidence, III), which: 1) targets the cytokine storm and T-cell proliferation using etoposide (75-100 mg/m², corticosteroids, polyvalent immunoglobulins (therapeutic dosing), and, when the first hit is unsuccessful, salvage regimens such as liposomal doxorubicin, etoposide, and methylprednisolone (DEP), alemtuzumab-based therapy, or cytokine adsorption using therapeutic cytokine-adsorption columns or plasmapheresis⁶³⁻⁶⁵; and 2) targets neoplastic disease by specific treatment as soon as organ function is re-established or, at the least, has improved to an acceptable degree.

It must be noted that this is an expert opinion, because no standard-of-care or prospective validation studies of therapy for M-HLH in adult patients have been conducted. The treatment suggestions detailed above are targeted to suppress hyperinflammation, which is central to the pathogenesis of this entity. The suggestions are taken from the pediatric protocols HLH-94 and HLH-2004 with adjusted dosing, taking into consideration reduced bone marrow reserve and pre-existing comorbidities in adults^{2,19} (level of evidence, III). Furthermore, because multiple factors may precipitate HLH in adults with malignancies, a thorough workup to identify potential triggers is suggested for patients with M-HLH. An example of such a workup developed by the authors is provided in Table 2.

No adult-specific, frontline M-HLH prospective trials have been conducted in the United States. A recent report from China described the use of combination chemotherapy with DEP as a salvage therapy for adult patients with refractory HLH (level of evidence, IIA). The DEP regimen resulted in complete remissions in 27% and partial remissions in 49% of the 63 patients who received

TABLE 2. Suggested Adult Malignancy-Associated Hemophagocytic Lymphohistiocytosis Baseline Workup

- Ferritin, coagulation panel with fibrinogen; LDH, lactate, triglyceride, β 2-microglobulin, CRP, CBC with differential, peripheral smear review, CMP: order STAT
- Soluble IL2 receptor, cytokine panel (if available locally or as a send-out), soluble CD163
- Cultures blood, urine, sputum, bronchoscopy
- NK function and T-lymphocyte subsets by PB flow requisition
- Pregnancy test
- Serologies: EBV, CMV, HSV, acute hepatitis screen, parvovirus
- Viral loads: EBV, CMV, HHV-6, HHV-8, HIV, parvovirus, adenovirus if prior allo-SCT
- Other
 - Urine: Histoplasmosis antigen; serum quantiferon
 - DAT, ANA (other rheumatology workup if indicated)
 - Immunoglobulin panel (quantitative immune globulins, IgG subsets)
 - Transferrin saturation: If elevated, HFE gene analysis
- Imaging
 - PET-CT preferred over CT chest/abdomen/pelvis
 - MRI brain, possibly spine
- Biopsies (as clinically indicated to identify hemophagocytosis or diagnose/stage underlying tumor)
 - Bone marrow aspiration and biopsies
 - Lymph node aspiration by FNAC if palpable lymph nodes, consider excisional biopsy
 - Skin biopsies particularly if rash, livedo, skin lesions, normal vascular changes/red moles
 - Liver biopsy (if HLH liver involvement features)
 - Lumbar puncture (diagnostic and therapeutic) as soon as bleeding risk declines
- Hypomorphic mutation genetic testing: To be ordered when HLH diagnosis confirmed (if available locally or as a send-out)

Abbreviations: Allo-SCT, allogeneic stem cell transplantation; ANA, antinuclear antibody, CBC, complete blood count, CMP, comprehensive metabolic panel, CMV, cytomegalovirus; CRP, C-reactive protein, CT, computed tomography; DAT, direct antiglobulin testing, EBV, Epstein-Barr virus; FNAC, fine-needle aspiration cytology; HFE, human factors engineering, HHV, human herpes virus; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; IgG, immunoglobulin G; IL2, interleukin 2; LDH, lactate dehydrogenase; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NK, natural killer, PB, peripheral blood; PET-CT, positron emission tomography-computed tomography.

treatment for refractory HLH.⁶⁵ These are encouraging results, but the DEP regimen is difficult to use in already myelosuppressed and immunocompromised adults who have M-HLH. The incorporation of novel noncytotoxic agents that are less prone to add cumulative toxicity and myelosuppression to chemotherapy for the underlying malignancy may help alleviate the problem.

Novel Therapies for HLH

Recently, it was demonstrated that alemtuzumab is an effective salvage therapy for refractory HLH, leading to improved response rates and a higher rate of transition to allogeneic stem cell transplantation in pediatric patients.⁶⁶ A clinical trial of alemtuzumab up-front in combination with dexamethasone and etoposide has been developed

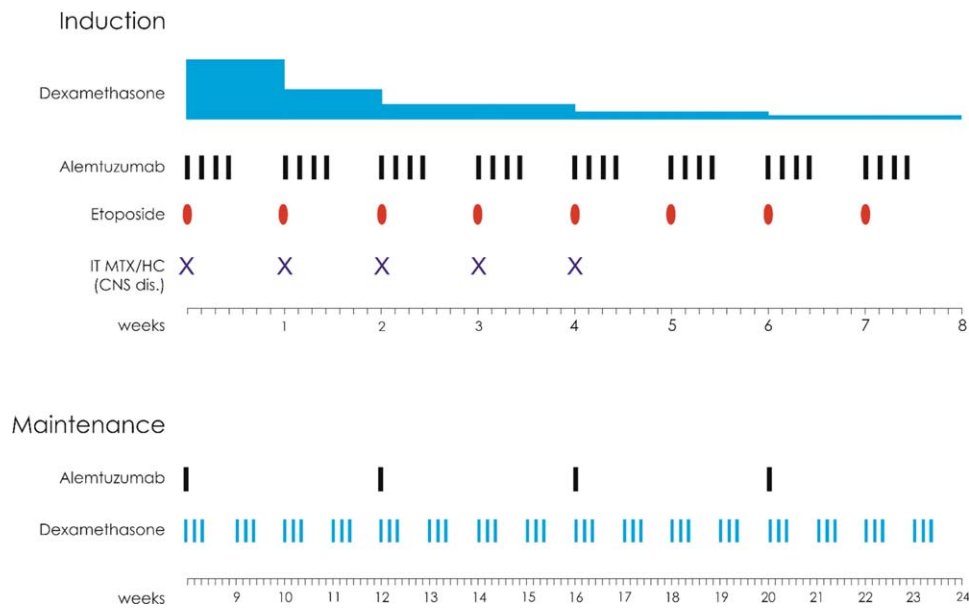


Figure 3. Alemtuzumab in combination with etoposide and dexamethasone for the treatment of adult patients with secondary hemophagocytic lymphohistiocytosis is illustrated. CNS dis. indicates central nervous system disease; IT MTX/HC, intrathecal methotrexate and hydrocortisone.

for the treatment of adults with HLH and is ongoing (clinicaltrials.gov identifier NCT02385110) (Fig. 3).

Another novel HLH therapy is the IFN- γ inhibitor NI-0501, which could be a major breakthrough in the therapy of secondary and M-HLH.⁶⁷ NI-0501 is a humanized anti-IFN- γ monoclonal antibody that binds to and neutralizes IFN- γ . NI-0501 is in clinical trials for primary HLH as the first targeted monoclonal therapy for HLH. Thirteen children with primary HLH have been treated with NI-0501 (12 as second-line treatment and 1 as first-line treatment; level of evidence, IIA). Significant improvements in HLH parameters were noted in 9 of the 13 patients, and 7 patients proceeded to allogeneic stem cell transplantation. Eleven of 13 patients were alive at 8 weeks, and IFN- γ neutralization was demonstrable. Therapy was well tolerated, with none of the typical short-term or long-term toxicities reported with etoposide-based regimens. NI-0501 appears to be a nonmyelosuppressive drug that may have the potential to improve responses and tolerability in adult M-HLH as frontline or salvage therapy.

Ruxolitinib is a Janus kinase 1 (*JAK1*)/*JAK2* inhibitor that has shown activity in inflammatory conditions. It is approved by the US Food and Drug Administration for the treatment of myelofibrosis and polycythemia vera and has demonstrated activity in corticosteroid-resistant, acute graft-versus-host disease.⁶⁸ Ruxolitinib had efficacy in

reducing immunopathology and in prolonging survival in murine models of HLH.^{69,70} Also in murine models, treatment with ruxolitinib significantly lessened the clinical and laboratory manifestations of HLH, including weight loss, organomegaly, anemia, thrombocytopenia, hypercytokinemia, and tissue inflammation. The investigators further demonstrated that in vivo exposure to ruxolitinib inhibited signal transducer and activator of transcription (*STAT*) activation, suppressed CD8-positive T-cell expansion, and reduced proinflammatory cytokines and concluded that *JAK-STAT* inhibition may be a novel approach to mitigating cytokine-mediated hyperinflammation in HLH. It is plausible that ruxolitinib could be used alone in M-HLH without causing the same degree of myelosuppression or immunosuppression caused by etoposide-based or alemtuzumab-based therapies. Alternatively, this agent may be effective in combination with standard HLH lympholytic therapies to improve response rates or time to response to induction therapy, or as a maintenance therapy to reduce relapse, especially among patients who are not candidates for allogeneic stem cell transplantation for HLH. An ongoing pilot study of ruxolitinib in secondary HLH may help better define its role in patients who have secondary disease, including M-HLH (clinicaltrials.gov identifier NCT02400463; level of evidence, III).

An international collaborative effort to improve the awareness, diagnosis, early referral, and therapy of M-

HLH is needed. Improved awareness and use of emerging novel therapies, such as inhibitors of IFN- γ and JAK-STAT pathways, in rationally developed clinical trials, either alone or in combination with T-lympholytic and immunosuppressive agents, may allow us to improve outcomes in this difficult condition.

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