Special Article

Recommendations for the Use of Etoposide-Based Therapy and Bone Marrow Transplantation for the Treatment of HLH: Consensus Statements by the HLH Steering Committee of the Histiocyte Society

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Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome requiring aggressive immunosuppressive therapy. Following 2 large international studies mainly targeting pediatric patients with familial disease and patients without underlying chronic or malignant disease, the HLH-94 protocol is recommended as the standard of care when using etoposide-based therapy by the Histiocyte Society. However, in clinical practice, etoposide-based therapy has been widely used beyond the study inclusion criteria, including older patients and patients with underlying diseases (secondary HLH). Many questions remain around these extended indications and published reports do not address several practical issues. To tackle these concerns, the HLH Steering Committee of the Histiocyte Society decided to issue guidance for use of the HLH-94 protocol. The group convened in a structured consensus finding process to define recommendations that are based largely on expert opinion backed up by available data from the literature. The recommendations address all main elements of HLH-94 including corticosteroids, cyclosporin, etoposide, intrathecal therapy, and hematopoietic stem cell transplantation (HSCT) and consider various forms of HLH and all age groups. Aspects covered include indications, applications, dosing, side effects, duration of therapy, salvage therapy, and HSCT. These recommendations aim to provide a framework to guide treatment decisions in this severe disease. © **2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;■:■-■)**

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Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome marked by the uncontrolled activation of lymphocytes and macrophages and resulting in excessive cytokine production and tissue infiltration. HLH is defined by a characteristic combination of clinical and laboratory features (Table I) and can be regarded as a common manifestation of a group of hyperinflammatory conditions with variable pathogenesis.[1] The best-defined risk factors for HLH are

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Abbreviations used
AML- Acute myeloid leukemia
BSA- Body surface area
CNS- Central nervous system
CSA- Cyclosporin
EBV- Epstein-Barr virus
FHL- Familial hemophagocytic lymphohistiocytosis
HIV- Human immunodeficiency virus
HLH- Hemophagocytic lymphohistiocytosis
HSCT- Hematopoietic stem cell transplantation
MAS- Macrophage activating syndrome
NK- Natural killer

mutations in genes regulating lymphocyte cytotoxicity.[2] However, a number of other conditions can be associated with HLH including malignant, rheumatic and metabolic diseases, and immunodeficiencies. Notably, infections can trigger HLH in all these disorders,[3] but can also be the only disease-associated factor. HLH can develop at all ages.

Without treatment, the prognosis of HLH is poor.[4] The introduction of etoposide was the first major advance in the treatment of this disease. The etoposide-based treatment protocol HLH-94 consisted of 8 weeks of induction therapy and subsequent continuation therapy until HSCT for patients with familial, relapsing, or severe and persistent HLH.[5] It resulted in a 5-year survival of 54%. The recently published results of the subsequent HLH-2004 protocol confirmed this efficacy and showed that upfront cyclosporin (CSA) and intrathecal corticosteroids do not further improve treatment results.[6] Overall 5-year survival in HLH-2004 was 62%, but this was not statistically significant from the HLH-94 results. Based on these results, the HLH Steering Committee of the Histiocyte Society decided to recommend the use of the HLH-94 protocol (Figure 1) as the standard of care if using etoposide-based therapy for HLH (Histiocyte Society Meeting, Singapore, September 2017). Antithymocyte globulin has shown similar efficacy in a single center study,[7] and promising preliminary data have been generated with alemtuzumab[8] and emapalumab (anti-interferon gamma),[9] but these alternative approaches are not further discussed in this consensus paper.

Both HLH-94 and HLH-2004 targeted pediatric patients with familial disease (documented by affected siblings and/or a molecular diagnosis in familial hemophagocytic lymphohistiocytosis [FHL] causing genes) and patients without underlying chronic or malignant disease, who fulfill diagnostic criteria for HLH.[5,6] However, in clinical practice, the protocols have been used widely beyond the study inclusion criteria.[10,11] Many questions remain around these extended indications. Furthermore, the published reports leave a number of unanswered questions surrounding indication and application, dosing and side effects, duration of therapy, salvage therapy, and HSCT. Moreover, the use of HLH-94 therapy is complicated by the need to adapt to the variable clinical course, the risk of treatment-related morbidity, and disease recurrence.[12]

On the basis of these considerations, the HLH Steering Committee of the Histiocyte Society decided to issue detailed recommendations for the use of the HLH-94 protocol. The group convened in a structured consensus finding process to issue recommendations that are essentially based on expert opinion in addition to the published HLH-94 and HLH-2004 data.

METHODS

Selection of contributors

The authors represent the 11 current members of the HLH Steering Committee of the Histiocyte Society (www.histiocytesociety.org), a nonprofit organization of physicians and scientists from around the world committed to improving the lives of patients with histiocytic disorders. The current head of the HLH Steering Committee (S.E.) served as coordinator. Four additional physicians were recruited for this project to achieve a more balanced subspecialty representation. Overall, the following medical subspecialties were represented (some authors represent several disciplines): pediatric hematology/oncology (9), adult hematology/oncology and internal medicine (3), pediatric immunology (3), pediatric rheumatology (2), pediatric infectious diseases (1), and pediatric critical care (1).

Procedure

This document summarizes consensus-based recommendations that were developed by this group of experts in a structured consensus finding process. The recommendations are essentially based on expert opinion backed up by available literature data. After the definition of the scope of the project, individual recommendations were proposed by all members of the group and discussed by e-mail, and then selected and structured in a telephone conference. After a further round of refinement by e-mail, each recommendation was discussed, refined in its exact phrasing and voted on in a personal meeting (HS meeting, Singapore 2017). The consensus strength for each of the statements was classified as follows:

- Strong consensus >95% of participants agree
- Consensus >75% to 95% of participants agree
- Majority agreement >50% to 75% of participants agree
- No consensus ≤ 50% of participants agree

The comments following each of the recommendations were drafted by 1 to 3 group members, modified by an e-mail exchange within the group and integrated into the manuscript by the coordinator, followed by a consensus discussion in a final telephone conference (January 2018).

Disease definition

The clinical diagnosis of HLH currently relies on criteria that were originally defined in the context of treatment studies. The HLH-94 study recruited patients <16 years of age, who fulfilled 5 of 5 diagnostic HLH criteria (fever, splenomegaly, cytopenia in 2 of 3 lineages, elevated triglycerides or decreased fibrinogen, and hemophagocytosis) or had a familial history in combination with a clinical picture suggestive of HLH in the absence of a known malignant disease.[5] In the HLH-2004 protocol, ferritin, natural killer (NK) cell activity, and soluble CD25 were added as new diagnostic criteria.[13] HLH-2004 inclusion required 5 of 8 diagnostic criteria, and/or a molecular diagnosis of diseases associated with defects in lymphocyte cytotoxicity (FHL type 2-5, Chediak-Higashi syndrome, Griscelli syndrome type 2, or X-linked lymphoproliferative disease). Patients <18 years with no underlying disease and no prior cytotoxic or CSA treatment were recruited.[6]

This set of criteria, the cutoffs used for the laboratory parameters, as well as the nomenclature and classification of HLH are currently debated and modifications have been discussed. For this article, HLH is defined according to the diagnostic criteria used in the HLH-2004 trial (Table I). The term "primary HLH" is used for patients with disease-causing mutations in the genes encoding perforin (FHL2), Munc 13-4 (FHL3), Syntaxin 11 (FHL4), Munc 18-2 (FHL5), Lyst

TABLE I. Diagnostic criteria for HLH used in the HLH-2004 trial

HLH-2004 diagnostic criteria
The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled:
1. A molecular diagnosis consistent with HLH is made
2. Diagnostic criteria for HLH are fulfilled (5 of the 8 criteria below)
Fever
Splenomegaly
Cytopenias (affecting ≥2-3 lineages in the peripheral blood):
Hemoglobin <90 g/L (in infants <4 wk of age, hemoglobin <100 g/L)
Platelets $<100 \times 10^9$/L
Neutrophils $<1.0 \times 10^9$/L
Hypertriglyceridemia and/or hypofibrinogenemia:
Fasting triglycerides ≥ 3.0 mmol/L (ie, ≥ 265 mg/dL)
Fibrinogen ≤ 1.5 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin ≥ 500 μg/L
Soluble CD25 (ie, soluble IL-2 receptor) ≥ 2400 U/mL

HLH, Hemophagocytic lymphohistiocytosis; *NK*, natural killer.

(Chediak-Higashi syndrome), and Rab 27A (Griscelli syndrome type 2), patients with a positive family history, as well as for HLH evolving in patients with mutations in the genes encoding for signaling lymphocyte activation molecule associated protein (XLP1) and X-linked inhibitor of apoptosis (XLP2).[2] The term MAS-HLH (MAS = macrophage activating syndrome) is used for patients with underlying rheumatic disorders[14] including autoinflammatory diseases.[15] The term "secondary HLH" is used for patients with other underlying diseases. This includes infections in the absence of disease-causing mutations in the mentioned genes,[16] rheumatological conditions, malignancies,[17,18] metabolic diseases,[19,20] or inherited or acquired immunodeficiencies.[21]

Providers for whom these recommendations are intended

These recommendations are intended for all physicians, who are confronted with a patient fulfilling HLH criteria (as defined in the HLH-2004 trial) and who are considering treating their patient(s) with an etoposide-based treatment regimen. The basis of these recommendations is the use of the HLH-94 protocol including induction phase, continuation phase, and proceeding to HSCT if indicated.

Recommendations on the use of the HLH-94 protocol

Indication and application.

1. Rapid application of the HLH-94 protocol, including use of etoposide, can be lifesaving in patients with HLH. [Strong Consensus]

This statement is valid for patients with primary HLH,[5,6] as well as some patients with severe secondary HLH.[5,6,22-26] Because of the rapid progression of disease manifestations, early initiation of therapy is imperative to achieve the best outcomes.[23,27] A decision on whether or not to use elements of the HLH-94 protocol, including etoposide, is often required before definite diagnosis of primary HLH.

2. It is strongly recommended to use HLH-94 in close consultation with an expert experienced in the treatment of HLH. [Strong Consensus]

Because of the rarity and severity of HLH and the potential treatment-related toxicities that are frequently difficult to distinguish from the manifestations of HLH itself,[12] the use of the HLH-94 protocol,[5] in particular of etoposide, requires careful guidance.

3. The decision to administer HLH-94 relies on the severity of the clinical evolution and not solely on the fulfillment of ≥5 of 8 HLH criteria. There are cases of HLH that fulfill less than 5 of 8 criteria, but nevertheless would benefit from timely application of HLH-94 (eg, central nervous system [CNS] HLH). Also, not all patients with HLH require etoposide, even if 8 of 8 criteria are fulfilled. [Strong Consensus]

Fulfillment of ≥5 of 8 HLH criteria defined in the HLH-2004 trial (Table I) serves as a practical tool for HLH diagnosis. The individual criteria themselves are not specific for HLH and can frequently be seen in other inflammatory responses, including those in critically ill patients with multiorgan dysfunction syndrome. It is the constellation of the criteria that should raise suspicion for the diagnosis of HLH. Not all criteria may be present in the early phase and, importantly, hemophagocytosis is not necessary for the diagnosis of HLH.[1,28] HLH-2004 criteria may not be optimal for patients with secondary HLH, including MAS-HLH,[26,29,30] or adults with HLH.[10,31] The severity and progression of disease manifestations rather than the fulfillment of the HLH criteria *per se* are critical for the decision of when to initiate the HLH-94 protocol. They include manifestations that are not a formal part of the HLH-2004 criteria such as neurologic symptoms, cerebrospinal fluid pleocytosis, conjugated hyperbilirubinemia, elevated transaminases, hypoalbuminemia, hyponatremia, or elevated D-dimers.[1] In cases of isolated CNS disease, patients often do not meet ≥5 of 8 HLH criteria.[32] Published[33] and unpublished experience indicate that they will benefit from timely HLH-94 therapy. In contrast, less severe cases may only require corticosteroids with or without intravenous immunoglobulins (IVIG)[34] to control HLH disease manifestations, especially some patients with secondary HLH or MAS-HLH.

4. Germline mutations consistent with familial HLH represent a condition that predisposes to HLH. HLH-94 should only be used if the patient develops the clinical syndrome of HLH. [Strong Consensus]

A molecular diagnosis of primary HLH *per se*, although part of the diagnostic criteria for the HLH-2004 study, is not an indication to start HLH-94 therapy. In the absence of symptoms, patients must be carefully monitored and treatment should be initiated rapidly once symptoms develop. Some group members use cyclosporin A as prophylaxis before HSCT, for example, in siblings of patients with primary HLH identified as asymptomatic carriers of severe biallelic mutations at birth.

5. In all patients with newly diagnosed HLH, a thorough search for underlying or associated conditions (eg, infection, malignancy, autoimmune or autoinflammatory disease, metabolic disease, immunodeficiency) must be undertaken. Findings may dictate alternative or adjunctive treatment for HLH. [Strong Consensus]

Underlying or associated conditions may trigger HLH and maintain the immune activation.[12,13] Viral infections, in particular

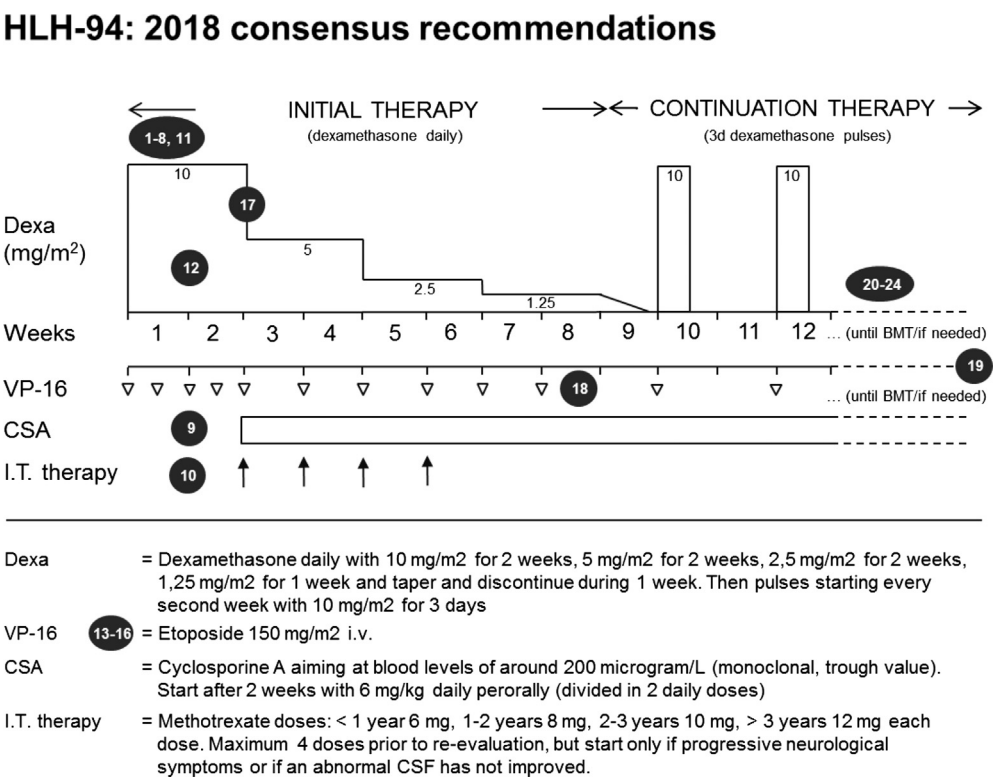

FIGURE 1. HLH-94: 2018 consensus recommendations. *BMT,* Bone marrow transplantation; *CSF,* cerebrospinal fluid; *HLH,* hemophagocytic lymphohistiocytosis.

Epstein-Barr virus (EBV) infections, are the most common triggering factor of primary HLH[6,35] and infection-associated secondary HLH.[31] In severe EBV-HLH, there may be a window for observation, corticosteroid/CSA, and IVIG treatment. In addition, targeting the EBV reservoir by B-cell depletion (rituximab) has therapeutic value.[36] However, if disease evolution is severe and/or refractory to such therapy, prompt introduction of etoposide is recommended.[22,23,25,37,38] Another common form of virus-associated HLH is human immunodeficiency virus (HIV)-HLH, and in a study of 58 HIV-infected adults with HLH, 24 patients (41%) were reported to have received etoposide alone or in combination with corticosteroids.[39] The value of HLH-94 is less known in other forms of infection-associated HLH and care must be taken to differentiate neutropenic bacterial sepsis from HLH.[40] HLH-94 is not indicated in leishmaniasis and tuberculosis.[41,42]

There may be more than 1 potential trigger. MAS-HLH may evolve with or without triggering infection in patients with underlying rheumatic disorders and can be the initial clinical presentation. In MAS, IL-1 inhibitors (anakinra) represent a valuable addition to cyclosporine and corticosteroids, and HLH-94 is not considered first-line treatment.[30,43]

Special consideration for possible lymphoma and appropriate workup is required. Viral reactivation or chronic active EBV infection can be associated with lymphoma, and this represents an increasingly recognized lymphoma subtype in otherwise healthy individuals.[44] In malignancy-associated HLH, a regimen including etoposide and corticosteroids may be valuable before or concomitant with start of tumor-specific treatment.[10,17,18,45]

In patients with suggestive features, underlying metabolic or immunodeficiency disorders should also be evaluated. The HLH-94 protocol is not the treatment of choice for immunodeficiencies, but has been used successfully in patients with chronic granulomatous disease.[21] Notably, the treatment of concomitant conditions is essential in HLH whether or not the HLH-94 protocol is used. Importantly, in case of severe or quickly deteriorating clinical presentation, the search for underlying or associated conditions should not delay treatment decisions because prompt initiation of HLH-directed treatment can be vital.[1,46]

6. Most adult patients with HLH have an underlying triggering condition, in particular infection or malignancy. Although the treatment of the underlying condition has priority, etoposide can be the drug of choice for control of the HLH manifestations in certain cases. [Strong Consensus]

HLH is not only a pediatric disease and is still underdiagnosed in adults.[10,31] Most adult patients with HLH have an underlying condition, and broad screening for infection, malignancy, and rheumatic disease is indicated. However, although primary HLH is mainly a disease of childhood, late presentations in adulthood have been reported.[47] Functional and genetic screening for primary HLH can therefore be indicated in patients without an obvious trigger or with risk factors such as consanguinity, familial disease, or features of albinism. The treatment of HLH in adults is mainly directed against the underlying condition, but corticosteroids and IVIG, and etoposide in severe cases, should not be withheld to control the hyperinflammation.

7. In patients with suspected or confirmed HLH, in whom the decision to treat with HLH-94 is deferred, the clinical situation must be re-evaluated at least daily. [Strong Consensus]

This principle is particularly relevant for patients in intensive care units.[48] They require frequent re-evaluation of disease parameters, in particular clinical assessment of hepatosplenomegaly and neurological status, blood counts, as well as parameters of liver disease and coagulation, often every 6 to 12 hours.

8. HLH-94 therapy is not the primary approach for patients with MAS-HLH. However, although other antiinflammatory drugs are effective in most cases, etoposide remains a relevant choice for some patients with severe or refractory disease. [Strong Consensus]

MAS-HLH describes a potentially life-threatening complication of systemic inflammatory disorders, most commonly in systemic onset juvenile idiopathic arthritis, but also in many other autoimmune or autoinflammatory conditions. Although a set of classification criteria for MAS differing from the HLH-2004 criteria has been established,[29] patients with severe MAS-HLH may also fulfill HLH-2004 criteria.[49] Even then, HLH-94 is not the primary treatment choice. Patients with active disease despite corticosteroids, CSA, and/or anakinra represent a serious challenge. In refractory severe cases, etoposide may be the most effective drug.[24] Etoposide therapy should be discussed with an expert, and a dose reduction to 50 to 100 mg/m^2 may be appropriate.[50,51]

9. CSA is not recommended in the first weeks of HLH-94 therapy as this may induce toxicity. In patients with primary HLH who have achieved remission, CSA may be used to potentially prevent disease reactivation. [Strong Consensus]

Because CSA had been reported to inhibit production of IFN-γ and to be beneficial in initial HLH treatment,[52,53] it was started upfront in the HLH-2004 protocol instead of at week 9 in HLH-94. Because this modification did not significantly improve outcome,[6] CSA is not recommended in the first weeks as—in conjunction with full-dose dexamethasone—this may lead to substantially elevated blood pressure. Posterior reversible encephalopathy syndrome is associated with CSA,[54] but it was only mentioned in 2 serious adverse event reports in the HLH-2004 study.[6] Although CSA is a potent inhibitor of T-cell activation,[55] there is no evidence documenting that CSA can prevent disease reactivation in patients who have achieved remission. A majority of authors nevertheless use CSA as a bridge to HSCT in primary HLH, starting not earlier than week 3, when dexamethasone is tapered. Lower trough levels (120-150 μg/L) may help to minimize toxicity.

10. Intrathecal methotrexate (MTX) therapy is recommended for patients with CNS involvement not improving during systemic HLH-94 therapy. The time point of treatment must balance the risks of treating versus waiting. [Strong Consensus]

CNS involvement is a critical prognostic factor in HLH.[56-58] In patients with neurological symptoms (including seizures, altered consciousness, facial or other never palsies, dysarthria, and dysphagia), and laboratory or imaging findings suggesting CNS involvement, it is of utmost importance to control CNS inflammation. CNS symptoms improve with systemic therapy alone in most cases, and data are insufficient to determine whether additional intrathecal therapy can further improve CNS inflammation. The HLH-94 protocol recommends weekly intrathecal MTX treatment for patients with neurological signs or symptoms persisting after 2 weeks of systemic therapy for 3-4 doses prior to re-evaluation, preferably until all cerebrospinal fluid (CSF) indices and CNS symptoms normalize. Surveillance CSF analyses should be obtained for 2 to 3 weeks afterwards and later if any symptoms reoccur.[32] In HLH-2004 intrathecal prednisolone was added, but did not show additional benefit. Considering the good CSF penetration of high-dose dexamethasone,[59] intrathecal MTX alone is recommended.

11. HLH-94 therapy can be indicated in patients with primary HLH who present with isolated CNS disease. [Strong Consensus]

In patients with genetic predisposition to primary HLH, CNS disease can occur in the absence of any of the clinical and systemic laboratory criteria defining HLH.[60-65] These patients may present with variable symptoms and CSF abnormalities leading to diagnoses such as encephalitis, atypical cerebral vasculitis, CNS lupus, acute necrotizing encephalopathy, multiple sclerosis, or acute disseminated encephalomyelitis. Therapies for these diagnoses are usually not sufficient to control isolated CNS-HLH. Unpublished evidence suggests that systemic therapy such as the HLH-94 protocol may be required.

12. In patients receiving HLH-94, supportive treatment is strongly recommended, in particular against *Pneumocystis jiroveci* and broad antifungal prophylaxis. [Strong Consensus]

The combination of high-dose corticosteroids, etoposide, CSA, and the use of additional drugs directed at the underlying cause such as rituximab or antineoplastic drugs cause significant immunosuppression. Antifungal prophylaxis should include prophylaxis against *P jiroveci*[66] and drugs suitable for the prevention of aspergillosis.[67] Weekly tests for infections or reactivation of pertinent triggers are recommended (EBV, cytomegalovirus, adenovirus, fungi).

Dose adaptations and side effects.

13. HLH-94 treatment may have to be individualized *a priori* depending on the clinical context (including underlying condition, age). Cytopenias or liver disease is not a contraindication for initiation of treatment with etoposide. [Strong Consensus]

The dosing regimen in HLH-94 can be altered to adjust drug doses and/or the dosing intervals.[13,50,68] *A priori* adjustment may be justified in secondary HLH. For example, children with secondary HLH and a milder clinical course still requiring HLH-94 therapy can be started on etoposide 150 mg/m^2/dose once weekly.[68] Reduced etoposide of 50 to 100 mg/m^2/dose once per week may also be considered in older teenagers and adults.[10,69] Depending on patient response, more or less than 8 weeks of therapy may be needed.[50,68] The presence of cytopenias and/or liver dysfunction should not prevent initiation of etoposide therapy as both bone marrow and liver dysfunction secondary to disease typically improve with HLH-directed therapy.

14. When using the HLH-94 protocol, etoposide dosages should be calculated per m^2 also in children less than 10 kg. [Majority Agreement]

Dosing of chemotherapeutic drugs including etoposide is frequently adjusted in infants with a body weight below 10 kg by changing from dosing per body surface area to dosing per kilogram body weight. However, the HLH-94 and HLH-2004 protocols specified etoposide doses per m^2 also in infants less than 10 kg, and the majority of response data in patients with HLH have been obtained with this dosing. Pharmacological studies also support dosing of etoposide per m^2.[2,70,71] However, several centers have successfully

used etoposide at a dose of 5 mg/kg in infants weighing less than 10 kg and continue recommendation of these lower doses.

15. Because etoposide is mainly cleared by the kidneys, dose reduction is recommended if renal function is impaired, based on age-specific norms. The following dose reductions can serve as a guideline for initial dosing:
    - 25% etoposide reduction if creatinine clearance is 20-40 mL/minute/1.73 m^2 body surface area (BSA)
    - 50% etoposide reduction if creatinine clearance is <20 mL/minute/1.73 m^2 BSA
    - 75% etoposide reduction if creatinine clearance is <20 mL/minute/1.73 m^2 BSA, and conjugated bilirubin is >50 μmol/L (ie, >3 mg/dL)

    No dose reduction of etoposide is recommended for isolated hyperbilirubinemia and/or elevated transaminases. [Strong Consensus]

Creatinine values have to be monitored during etoposide treatment and elevated values warrant measurement of creatinine clearance and consideration of dose adjustments. The limited literature on etoposide dosing in patients with abnormal kidney function indicates a significant correlation between etoposide plasma clearance and creatinine clearance.[72-74] Age-related normal values for creatinine clearance in infants must be considered.[75] Obstructive jaundice may further impair clearance, but only in the context of impaired renal function.[70,76] Because etoposide may be lifesaving, we do not recommend holding it entirely, as one may do with renal failure in other contexts. Some authors have noted that hypoalbuminemia may heighten toxicity due to increased unbound etoposide.[77-79] However, because uncontrolled HLH typically causes hypoalbuminemia and data are too limited, we do not recommend albumin-based dose adaptations.

Guidelines for dose adjustment are based on limited data, and further adjustments may be needed if excessive myelosuppression is evident. This should consider that cytopenias and liver disease can be side effects of etoposide therapy,[77,80] but also reflect disease activity.[28,35,81] Serial assessment of inflammation markers may aid in interpretation of ongoing/worsening cytopenias or hepatoxicity. The decision to adjust etoposide dosing should ideally be made in expert consultation. A normo- or hypercellular bone marrow argues against etoposide-induced bone marrow toxicity, and a hypocellular marrow can be a consequence of disease activity and/or treatment toxicity.

16. Current evidence indicates that the risk of developing acute myeloid leukemia (AML) after HLH-94 therapy is lower than the morbidity and mortality associated with severe HLH. [Strong Consensus]

The risk of developing treatment-related AML in the HLH-2004 and HLH-94 studies was 0.3% (1/368) to 0.4% (1/249) at a median follow-up of 5.2 and 6.2 years, respectively.[6,35] In a Japanese study of 81 patients with EBV-HLH treated with a median cumulative etoposide dose of 1500 mg/m^2 BSA, with a median follow-up of 44 months, only 1 patient developed acute therapy-related AML.[82] Overall, this risk is much lower than the risk of mortality associated with uncontrolled HLH.

Salvage therapy.

17. Although disease reactivations may be treated with reintroduction or reintensification of HLH-94, persistence of hyperinflammation and/or cytopenia warrants consideration of salvage therapy. [Strong Consensus]

In primary HLH, reactivations and/or persistence of hyperinflammation are frequent until curative HSCT has been performed.

Disease reactivation is especially common during the second half of the "Induction phase" of HLH-94,[12,13] when etoposide is administered once weekly and dexamethasone is reduced.[6] Such reactivations will commonly respond to a reintensification of therapy (such as a restart from week 2 of the protocol).[12,13] Intrathecal therapy is recommended for CNS reactivation. Reactivations may also occur after additional immune activation, for example, by infections. Antimicrobial therapy and IVIG should therefore be considered as supportive or therapeutic measures.[13] In the HLH-2004 study, there was an overrepresentation of deaths after 100 days in patients who had achieved resolution but then reactivated, stressing the importance of early HSCT.[6] Urgent HSCT should also be considered in patients with primary HLH if remission is difficult to achieve, to avoid disease progression and neurologic sequelae.[83,84]

Failure to respond to initial therapy is less common. If cytopenias (in particular thrombocytopenia $<40 \times 10^9$/L) and ferritin and/or sCD25 fail to respond after 2 weeks, the risk for an adverse outcome increases,[85] justifying consideration of alternative (salvage) therapy. When evaluating persistent cytopenias, etoposide toxicity should be considered as the possible cause. When evaluating persistence of hyperinflammation, the potentially slow response rate of ferritin[86] (less so sCD25) should be considered. Specific recommendations for salvage therapy are difficult because of limited data. Consultation with an HLH expert is strongly encouraged before choosing and starting salvage therapy.[8]

Duration of therapy.

18. Application of HLH-94 in the context of HLH does not mean that 8 weeks of etoposide has to be given. [Strong Consensus]

In primary HLH, 8 weeks of initial therapy is usually followed by "continuation therapy" as a bridge to HSCT. In secondary HLH, "continuation therapy" is usually unnecessary. Decisions on stopping therapy should be made on an at least weekly basis. Most patients with secondary HLH achieving a complete response require less than 8 weeks of etoposide[51] (and unpublished experience).

19. In patients with primary HLH, 8 weeks of induction should be followed by continuation therapy until HSCT. [Strong Consensus]

"Continuation therapy" is only intended as a bridge to HSCT.[35] Therefore, patients not proceeding to HSCT are typically weaned off of therapy after achievement of disease control. In patients with an HSCT indication, "continuation therapy" is recommended, although there is no evidence whether it will prevent reactivation/relapse. Most panel members continue etoposide as foreseen by the HLH-94 protocol also in patients with full remission. The minority of panel members prefer stopping etoposide and dexamethasone once full remission is achieved and advocate CSA alone until HSCT. They favor this approach especially if a donor is not immediately available, considering long-term sequelae of etoposide and large corticosteroid doses.

HSCT.

20. Allogeneic HSCT is currently the only option for long-term cure in primary HLH. Early conversations with an HSCT specialist should be undertaken in all cases of confirmed genetic HLH. [Strong Consensus]

Patients with primary HLH carry a high risk of reactivation that persists lifelong, even after control of the acute HLH episode. Accordingly, replacement of the defective immune system via allogeneic HSCT is currently the only curative approach. Decisions about transplantation are complex and influenced by many factors such as patient age, genetic subtype, HLH disease status, stem cell source, and donor availability.[83,87] Thus, conversations with disease and HSCT experts should begin soon after a diagnosis of primary HLH.

Because not all genetic etiologies are well defined, severely reduced expression of relevant proteins or reduced lymphocyte degranulation, a positive family history, or persistent/recurrent disease can be sufficient to establish the diagnosis of primary HLH. The demonstration of likely pathogenic germline variants in HLH-associated genes is not sufficient to diagnose primary HLH in the absence of additional evidence by functional assays or previous patient reports. In particular, a heterozygous or homozygous A91V perforin variant[88,89] in a patient with HLH is not a clear indication for HSCT, unless combined with a "severe" mutation.

21. Early HSCT should strongly be considered in asymptomatic carriers of biallelic HLH-associated mutations, if HLH has manifested in a family member in infancy. In other asymptomatic carriers of biallelic mutations in genes associated with familial HLH, the time point of transplantation should be discussed with an experienced center. [Strong Consensus]

Decisions regarding pre-emptive allogeneic HSCT for asymptomatic patients with HLH need to balance the risk of the procedure versus the risk of a wait-and-watch strategy. HSCT is warranted for the majority of asymptomatic affected siblings. For individual patients in a reliable health care setting, donor search followed by a conservative approach may be justified. In particular, patients with X-linked inhibitor of apoptosis deficiency present with a wide spectrum of clinical manifestations that do not necessarily lead to HLH[90,91] and outcome of HSCT may be poorer.[87] On the other hand, active HLH at the time of HSCT is correlated with a poorer outcome.[87] The HSCT indications and time point in these patients must be discussed with an experienced center.

22. Siblings and other relatives should be tested for the presence of HLH mutations before being considered as donors. Heterozygous mutation carriers are possible donors. [Strong Consensus]

Because the onset of HLH can vary between family members with the same mutations,[81,92] older age than the index patient without HLH manifestations is not sufficient to rule out the genetic disease. Currently, there is no evidence indicating that heterozygous siblings or parents of a homozygous or compound heterozygous index patient have an increased risk of developing HLH that would be transferred to the patient receiving the transplant.

23. In the absence of unambiguous genetic causes, familial history, and recurrent/refractory disease, there is no *a priori* indication for HSCT in HLH. The development of recurrent HLH warrants consideration for HSCT, if there is no clear explanation by a disease trigger that can eventually be controlled. [Strong Consensus]

Allogeneic HSCT is generally not used to treat patients with secondary HLH lacking identifiable germline mutations. Although treating the underlying trigger proves effective in many cases, in some patients the treatment response is suboptimal or not sustained. For these individuals, allogeneic HSCT may become a therapeutic option. This is particularly true for patients exhibiting sustained immunologic defects, such as reduced expression of perforin or signaling lymphocyte activation molecule associated protein (affected in X-linked lymphoproliferative disease) or diminished CD107a mobilization, in whom an underlying genetic defect is likely but may have escaped detection.[93]

24. HSCT should also be considered for adult patients with refractory/recurrent HLH in the absence of a treatable underlying condition and in patients with certain malignancies. [Strong Consensus]

Prospective data on HSCT in adults with HLH are lacking. Lymphoma-associated HLH and EBV-HLH are the main causes for HLH in adults. A considerable proportion are refractory or recurrent,[69,94] justifying consideration of allogeneic HSCT, even if only a haploidentical donor is available.[95] A comprehensive evaluation of potential donors is necessary to exclude related donors who are EBV-DNA positive or have decreased NK-cell degranulation. Recommendations are based on single center retrospective experience[95,96] and in case of malignancy-associated HLH adapted from recommendations for T-/B-cell lymphoma.[97,98] As HLH constitutes a dismal prognostic feature in patients with lymphoma, individual treatment decisions with regard to primary consolidation in chemotherapy-sensitive patients should be discussed with experienced centers. In the approximately 5% of adolescents/adults with primary HLH, HSCT is recommended according to pediatric guidelines. Approximately 10% of adult patients with HLH are without evidence of an underlying condition. In case of HLH recurrence, reinduction therapy with consolidating allogeneic HSCT in reinduction-sensitive patients is recommended.

SUMMARY AND CONCLUSIONS

Etoposide-based protocols are a valuable treatment option in patients with different forms of HLH. The use of the HLH-94 protocol, currently recommended for etoposide-based HLH therapy, requires careful guidance, in particular, if used beyond the indications of the HLH-94 and HLH-2004 study protocols. Moreover, morbidity and mortality of patients with HLH remained significant in these studies. Alternative treatment approaches are urgently needed and increasingly explored. However, until more data are generated and alternative drugs become widely available, our recommendations provide a helpful framework for the proper use of etoposide. Importantly, all statements in this text reflect the authors' experience and interpretation of current data (January 2018). They will need to be updated over time as more information becomes available.

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