Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies

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ABSTRACT

The hyperinflammatory syndrome hemophagocytic lymphohistiocytosis can occur in the context of malignancies. Malignancy-triggered hemophagocytic lymphohistiocytosis should be regarded seperately from hemophagocytic lymphohistiocytosis during chemotherapeutic treatment, which is frequently associated with an infectious trigger. The substantial overlap between the features of hemophagocytic lymphohistiocytosis with features of neoplasms makes its identification difficult when it occurs in malignant conditions. To facilitate recognition and diagnostic workup, and provide guidance regarding the treatment of malignancy-associated hemophagocytic lymphohistiocytosis, consensus recommendations were developed by the Study Group on Hemophagocytic Lymphohistiocytosis Subtypes of the Histiocyte Society, an interdisciplinary group consisting of pediatric and adult hemato-oncologists and immunologists.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) represents a spectrum of hyperinflammatory disorders associated with activation of cytotoxic T and natural killer (NK) cells, and macrophages. The excessive immune activation results in the clinical hallmarks of HLH, including fever, hepatosplenomegaly and cytopenias, combined with a characteristic set of laboratory parameters (elevated ferritin, triglycerides, soluble CD25, transaminases, lactate dehydrogenase, d-dimers; decreased fibrinogen, albumin, sodium). Hereditary or "primary" HLH is comprised of several genetically heterogeneous conditions, including familial HLH 2-5, Griscelli syndrome type II, and the X-linked lymphoproliferative syndromes, among others. Primary HLH predominantly occurs during childhood and may be triggered by an infection. As is the case with primary HLH, acquired or secondary HLH is not a stand-alone disease entity. Rather, secondary HLH represents a group of disorders that can occur under a variety of circumstances. The most frequent triggers are infection, in particular with viruses such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV). However, the disease can also be induced by certain malignancies, and autoimmune or autoinflammatory conditions. Due to their rarity, and the heterogeneity of inciting factors and clinical outcomes, the diagnosis and management of secondary forms of HLH has remained challenging. The substantial overlap between the features of HLH and features of neoplasms makes the identification of HLH when it occurs in the context of a malignancy very difficult. To facilitate recognition and diagnostic work up and provide guidance regarding the treatment of malignancy-associated HLH, the following consensus recommendations were created. These recommendations will not address HLH that occurs after hematopoietic stem cell transplantation.

Methods

The recommendations were developed by the Study Group on HLH Subtypes of the Histiocyte Society, an interdisciplinary group consisting of pediatric and adult hemato-oncologists and immunologists. Initially, the pertinent literature in Pubmed was reviewed. No randomized clinical trials, case control or cohort studies could be identified, which restricts the level of evidence to non-analytic studies and case series (level of evidence 4, based on the Oxford Centre for Evidence-Based medicine; *http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009*) or expert opinion (level of evidence 5). Subsequently, core statements were developed, critically revised and modified by the Study Group to achieve the highest possible agreement, which was classified as "full consensus" (100%) or "consensus" (≥80%). None of the core statements achieved a degree of consensus below 80%. The level of evidence and degree of consensus is specified in this document. Finally, the recommendations were written along with the core statements and reviewed by all authors.

General information

Core Statement 1 (level of evidence 5, full consensus): HLH can occur either as the initial manifestation of malignant disease (here referred to as "Malignancy-

 doi:10.3324/haematol.2015.123562
Manuscript received on April 7, 2015. Manuscript accepted on June 23, 2015.
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Triggered HLH") or in the setting of iatrogenic immunosuppression from chemotherapy ("HLH During Chemotherapy").

Hemophagocytic lymphohistiocytosis can occur in the context of a neoplasm under two different scenarios. First, it may be a presenting feature of the disease at onset or at relapse ("Malignancy-Triggered HLH"). Second, it can occur during, or shortly after, chemotherapeutic treatment for a malignancy ("HLH During Chemotherapy") while patients frequently are in remission from the malignancy. It is not completely understood why Malignancy-Triggered HLH occurs. Data generated using lymphoma cell lines suggest that secretion of cytokines (including interferon-γ and interleukin-6) by the malignant cells contributes to the development of hyperinflammation.[1,2] Elevated soluble CD25 is considered a marker of T-cell activity in HLH, as well as a marker that correlates with tumor burden in non-Hodgkin lymphoma.[3,4] In patients with Malignancy-Triggered HLH, viral infections may act as co-triggers. This is exemplified by EBV-associated lymphomas,[5] where both the virus and the lymphoma can drive HLH.

HLH During Chemotherapy, in the majority of cases, develops in association with triggering infections that occur as the result of chemotherapy-induced immunosuppression. The first connection of iatrogenic immunosuppresion with consecutive infection and HLH was shown in a series of patients receiving immunosuppressive treatment after kidney transplantation.[6] In contrast to infection-associated HLH in non-immunocompromised patients, where viruses are the major inciting pathogens, invasive fungi and bacterial infections may also play a substantial role in HLH During Chemotherapy.[7-10]

It is often difficult to differentiate between Malignancy-Triggered HLH and HLH During Chemotherapy, and these conditions may co-exist, such as in a patient with reactivation of a malignancy that also has an infection. In such situations, both the malignancy and the infection may contribute to the HLH.

Core Statement 2 (level of evidence 4, full consensus): Malignancy-Triggered HLH occurs most frequently but not exclusively with:

- **T-cell and NK-cell lymphomas or leukemias**
- **diffuse large B-cell lymphoma (DLBCL)**
- **Hodgkin lymphoma.**

The proportion of each tumor type in adult patients with HLH in the context of a neoplasm is reported to be 35% for T-cell or natural-killer (NK) lymphomas, 32% for B-cell lymphomas, 6% for leukemias, 6% for Hodgkin lymphomas, 14% for other and non-specified hematologic neoplams, 3% for solid tumors, and 3% for not specified neoplasms.[11] Large series suggest that, in adults, DLBCL is the predominant trigger in Western countries and Japan,[12,13] while T-cell neoplasms are the major cause in China and Korea.[14-16] In children, T-cell malignancies predominate.[17,18] T-cell cancers that are more likely to trigger HLH include peripheral T-cell lymphomas (particularly subcutaneous panniculitis-like T-cell lymphoma), primary cutaneous γδ-T-cell lymphoma,[19,20] anaplastic large cell lymphoma and, less commonly, lymphoblastic lymphomas.[17]

Diffuse large B-cell lymphoma is the most frequent neoplasm of B-cell origin that triggers HLH, especially in patients over 60 years of age. In Far East Asia, intravascular large B-cell lymphoma appears to have a special propensity to elicit HLH.[21] B-precursor neoplasms are not frequently reported.[10] In Hodgkin lymphoma, the occurrence of HLH is not confined to a specific subtype.[22,23] The prevalence of EBV as a co-trigger varies between up to 90% in Hodgkin lymphoma[5,24] to approximately 33% in peripheral T-cell lymphoma,[12,15] while it is low in DLBCL.[25,26]

Other malignant or non-malignant hematologic conditions that have been associated with HLH include EBV-associated T/NK-cell lymphoproliferative diseases predominantly found in Far East Asia,[27,28] Langerhans cell histiocytosis,[7] multicentric Castleman disease in HIV patients,[29] and cytophagic histiocytic panniculitis.[30]

Solid tumors are not commonly associated with HLH with only a 3% prevalence in adults.[11] In particular, mediastinal germ-cell tumors have been reported.[31] Interestingly, secondary malignant neoplasms (particularly acute myeloid leukemia) have been reported in patients after treatment of HLH, most likely attributable to high cumulative doses of the topoisomerase inhibitor etoposide; however, no recurrence of HLH has been reported in this context.[32]

Core Statement 3 (level of evidence 4, full consensus): HLH during chemotherapy is most frequently found during leukemia and lymphoma treatment, and during any phase of the therapy. It is frequently associated with an infectious trigger, including viruses, bacteria, and fungi.

In adult and pediatric oncology, aggressive therapies for malignant hematologic neoplasms carry the highest risk of developing secondary HLH. This is not restricted to induc-

Table 1. Diagnostic criteria.

HLH-2004 diagnostic criteria	
Feature	Cut off
1. Fever	
2. Splenomegaly	
3. Cytopenia	≥2 cell lines
Hemoglobin	< 90 g/L (neonates <100 g/L)
Platelets	$<100x10^9$/L
Neutrophils	$<1x10^9$/L
4. Hyperferritinemia	>500 μg/L
5. Hypofibrinogenemia	< 1.5 g/L
or hypertriglyceridemia	> 3 mmol/L
6. Elevated soluble CD25	> 2400 U/mL
7. Hemophagocytosis	Bone marrow, other tissues
8. Reduced or absent NK cytotoxicity	
Other features	
Elevated transaminases and bilirubin	
Elevated lactate dehydrogenase	
Elevated d-dimers	
Elevated cerebrospinal fuid cells and/or protein	

NK: natural killer cells.

tion and consolidation therapy but also occurs during maintenance.[8] The prevalence of an infectious trigger ranges from 75% to 100%.[7-10,33] Inflammatory toxicities thought to be due to pro-inflammatory cytokine release after administration of chimeric antigen receptor (CAR)-modified T cells and bispecific T-cell-engaging (BITE) antibodies for the treatment of B-precursor leukemias appear very similar to HLH, and may share some aspects of pathophysiology with HLH, as seen in more typical contexts.[34]

Core Statement 4 (level of evidence 4, full consensus): In a patient with HLH, the likelihood of an underlying malignant disease increases with age.

In adults, nearly half of the published cases were triggered by a neoplasm[11] and approximately 1% of adult patients with a hematologic malignancy develop HLH.[35] A large Japanese survey of 799 HLH patients evaluated the correlation between age and lymphoma as trigger. A lymphoma was found in 68% of patients aged over 60 years, in 38% aged 30-59, in 10% aged 15-29, and in 0% under 14 years of age.[12] In children and adolescents, a malignant context in HLH has a reported prevalence of 8%.[18]

Diagnostics

Here we consider 2 distinct clinical scenarios (Figure 1). First, an underlying malignancy must be excluded or confirmed in a patient with proven HLH. Second, HLH is suspected in a patient diagnosed with a malignant condition, initially or during treatment.

Core Statement 5 (level of evidence 5, full consensus): Currently, there are no generally accepted criteria for the definition of Malignancy-Triggered HLH or HLH During Chemotherapy. The HLH-2004 criteria may serve as a substitute definition, but they have substantial weaknesses.

The diagnosis of HLH is based on a set of clinical features and laboratory parameters. The first set of criteria was defined in the 1990s for pediatric patients of the international treatment HLH-94 study. It was later adapted for the subsequent HLH-2004 study.[36] The parameters that should be determined when HLH is suspected are listed in Table1. In the context of malignancy, several of these characteristics may be present and caused by the HLH and/or by the neoplasm (e.g. fever, organomegaly, cytopenias, elevated lactate dehydrogenase, and coagulation disturbances). Furthermore, elevation of ferritin must be differentiated from transfusion-related iron overload. Despite the term hemophagocytic lymphohistiocytosis, hemophagocytosis in the bone marrow, lymph nodes, or liver is neither a sensitive nor a specific finding in HLH,[37] and it may be present in several conditions related with malignancies, such as septicemia.

For clinical purposes, it is thus crucial to judge whether:
1. the combination
2. the extent, and
3. the progression of the mentioned clinical and laboratory abnormalities are unusual, unexpected, and otherwise unexplained.

For the purposes of definition and scientific classification of HLH, the HLH-2004 diagnostic criteria constitute the most widely used tool in pediatric and adult oncology. However, it must be noted that the development of these criteria was based on small pediatric data sets and expert opinion. Modifications have been suggested.[38,39] Takahashi et al. proposed diagnostic criteria for adult lymphoma-associated hemophagocytic syndrome on the basis of 142 cases, which have so far not gained wide acceptance. They include most of the HLH-2004 criteria, but in a slightly different composition, along with lactate dehydrogenase and d-dimers.[25,40] Importantly, the presence of an infection should not be regarded as contradictory to a malignant trigger. A scoring system was designed by Fardet *et al.*, based on a study with 312 adult patients with and without HLH and a 45% prevalence of hematologic malignancies.[41] The score is based on weighted features similar to the HLH-2004 criteria, intended to predict the likelihood of presence of HLH.

Temperature, spleen size, blood count, ferritin, fibrinogen, soluble CD25, and LDH can be used as markers of disease activity and treatment response. Platelets tend to rapidly reflect the level of HLH activity, with a drop in the platelet count indicating flares of disease. Ferritin rapidly increases in active HLH; however, levels normalize rather slowly following resolution of inflammation.[42] Here again, differentiation between the effects of the underlying neoplasm and HLH can be difficult. A repeat bone marrow aspirate may be indicated if cytopenias persist to determine whether they are related to treatment toxicity or active HLH.

Core Statement 6 (level of evidence 4, full consensus): In any patient with HLH, malignancy should be considered as a possible underlying disease.

An unidentified neoplasm can be the triggering factor in any patient with HLH, the most common being occult lymphomas. However, several factors modify this likelihood. While it is exceptionally rare in infancy, malignancy is the most frequent trigger in the elderly (*see Core Statement 4*). The diagnosis of another plausible trigger of HLH reduces the probability, but never excludes it. This also applies to the finding of pertinent infectious agents (e.g. EBV, CMV, Leishmaniasis). EBV is the most frequent trigger of acquired infection-associated HLH, and it is also frequently present in Malignancy-Associated HLH (e.g. in EBV-driven lymphomas).[5] In more than half of adult patients with HIV and HLH, an underlying malignancy, usually a lymphoma, can be found.[43] Autoimmune (e.g. systemic lupus erythematosus) and autoinflammatory diseases (e.g. systemic juvenile idiopathic arthritis, adult onset Still's Disease) may underlie HLH, with variable clinical overlap to malignancies, such as fever and cytopenias. A considerable diagnostic uncertainty with these diseases is quite common. In a patient with HLH and a rheumatological diagnosis, it is recommended to carefully search for a malignancy so any hidden neoplasm is not missed. The presence of a hereditary condition predisposing to HLH renders malignancy less likely, but does not exclude it (*compare Core Statement 8*).

Core Statement 7 (level of evidence 5, consensus): The required extent of diagnostic work up aimed at excluding a malignant condition (in particular an occult lymphoma) depends upon the likelihood that a malignancy might be present.

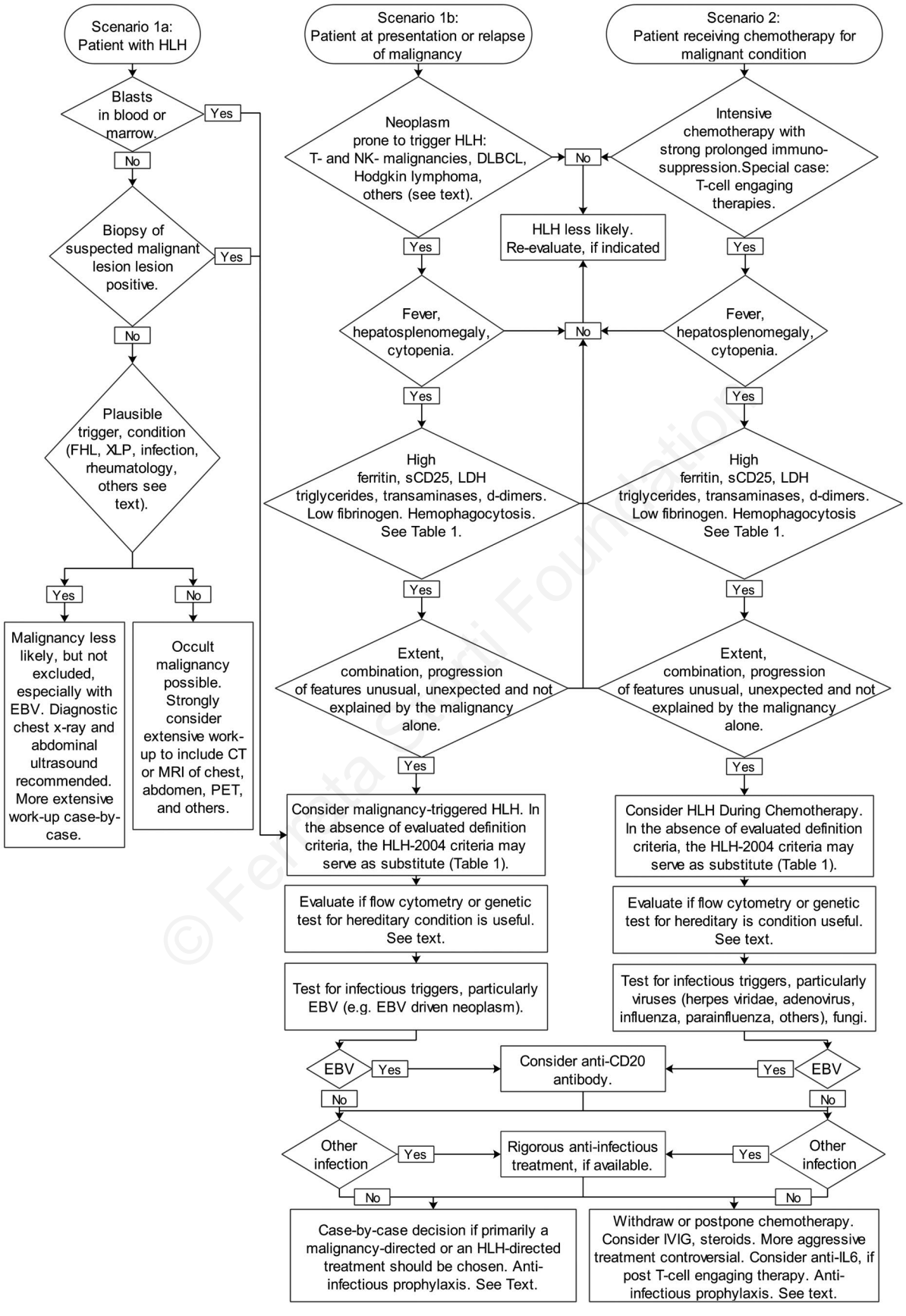

Figure 1. Flow chart for diagnosis and management of malignancy-associated hemophagocytic lymphohistiocytosis.

In all patients with HLH, the peripheral blood and the bone marrow should be screened for blasts. A chest X-ray, ultrasound and/or computed tomography of the abdomen and enlarged lymph nodes are recommended. Suspicious lymph nodes or cutaneous lesions indicative of lymphoma should be biopsied. In patients with elevated likelihood of malignancy (*compare Core Statement 6*), computed tomography, magnetic resonance imaging (MRI), and, in special cases, positron emission tomography[44] may be taken into consideration. Cerebrospinal fluid[45] should be screened for features of central nervous system involvement of HLH (elevation of protein and cell count, hemophagocytosis) and an MRI[46] of the brain should be strongly considered in patients with neurological signs and symptoms or in those with elevated protein and/or CSF cell count.

Core Statement 8 (level of evidence 4, full consensus): Malignancy-Triggered HLH has been described in patients with hereditary HLH and other primary immunodeficiencies. This association is most prominent in X-linked lymphoproliferative syndrome (XLP).

Several hereditary defects predispose to primary HLH (familial HLH type 2-5, Griscelli syndrome type 2, Chediak-Higashi syndrome, X-linked lymphoproliferative syndromes type 1 and 2, and others).[38] The age at onset of primary HLH is mostly in childhood. Nonetheless, it has been increasingly identified in adolescents and adults.[47] The decision as to whether a hereditary defect predisposing to HLH should be excluded in a patient with HLH in the context of malignancy should be taken on a case-by-case basis. This can be done by flow cytometric analysis as a measure to detect NK/T-cell degranulation defects and/or to determine the expression of relevant proteins [perforin, SAP (XLP1)]. Functional deficits should trigger HLH genetic testing to determine the exact genetic lesion.[48] Furthermore, an association with EBV susceptibility and lymphoma has been described for deficiency of magnesium transporter 1 (MAGT1), Interleukin-2-inducible T-cell kinase (ITK), and CD27. Patients with these disorders can display features resembling HLH. X-linked lymphoproliferative syndrome 1 (XLP1) is characterized by the triad of development of HLH most commonly at primary infection with EBV, hypogammaglobulinemia, and lymphoma. These manifestations can occur together or in isolation. In a retrospective analysis of 91 patients diagnosed with XLP1, 24% had had a malignant lymphoproliferative disorder, usually B-lineage non-Hodgkin lymphoma.[49] In male patients with lymphoma and EBV-driven HLH, genetic or flow cytometric analysis for XLP1[50] should thus be strongly considered. There is no evidence that XLP2 predisposes to malignancy.

In rare cases of HLH in the context of malignancy, mutations in HLH-associated genes can contribute to the development not only of the HLH, but also of the malignancy. For example, mice lacking perforin, the gene mutated in FHL2, are more susceptible to lymphoma.[51] Hypomorphic biallelic perforin mutations confer predisposition to late-onset HLH as well as hematologic malignancies.[52,53] The presence of the perforin variant A91V with a high allele frequency in the Caucasian population (4%-17% heterozygous carriers)[54-56] was initially reported to be more prevalent in 100 pediatric patients with acute lymphoblastic leukemia (ALL.)[56] A large study of 2272 children with ALL could not corroborate this finding in the general population of childhood ALL but supported it in a small subset of patients with BCR-ABL positive ALL.[55] Solid tumors (e.g. colorectal cancer and ovarian carcinoma) do not appear to be associated with perforin mutations.[57] Hodgkin lymphoma has been described in individuals with various genetic forms of HLH.[58-61]

Treatment

Core Statement 9 (level of evidence 5, consensus): in Malignancy-Triggered HLH:

- **it is uncertain whether primarily a malignancy-directed or an HLH-directed regimen should be used. This must be decided case by case;**
- **infectious triggers require rigorous treatment. Anti-infectious prophlyaxis (anti-fungal, *pneumocystis jiroveci*) and regular surveillance for secondary infections or reactivations (fungi, EBV, CMV) should be strongly considered in active HLH;**
- **anti-B-cell therapy (e.g. rituximab) may be considered in cases marked by highly replicative EBV infection.**

The mainstays of treatment of primary and infection-associated secondary HLH are immunoglobulins, glucocorticosteroids, cyclosporin A, and etoposide (VP16). A combination of the latter three has been used in the HLH-94 and HLH-2004 protocols.[36] Anti-thymocyte globuline (ATG) has shown efficacy in a cohort of mainly primary HLH patients[62] and alemtuzumab (anti-CD52) has been shown beneficial as a salvage agent in a limited number of patients.[63] Anti-interleukin-1 treatment can be used for HLH in auto-inflammatory conditions, in addition to glucocorticosteroids, cyclosporin A, and etoposide.[64]

The treatment of Malignancy-Associated HLH has not been prospectively studied. Due to the heterogeneity of patients and therapies in the published series,[14-16,65] no clear conclusions can be drawn as to whether an HLH-directed, malignancy-directed, or combined approach should initially be adopted. If an HLH-directed therapy is chosen, it must be followed by a neoplasm-directed protocol when the HLH resolves. A study of 162 adult patients with secondary HLH reported better survival after use of etoposide (in comparison to treatment directed at the underlying pathology or treatment with glucocorticosteroids only). However, due to the retrospective nature of the study, patients were not randomized and no separate analysis of the Malignancy-Triggered HLH subgroup (52%) was performed.[66]

In the murine model of familial HLH type 2 (perforin deficiency), mice with acute HLH receiving doxorubicin, clofarabine, cladribine, vinblastin, fludarabine, or L-asparaginase did not survive, while mice receiving etoposide, cyclophosphamide, or methotrexate did.[67] It is thus possible that lymphoma regimens containing the latter three agents treat both the HLH and the underlying neoplasm. Among these, etoposide is the substance for which clinical experience is greatest.[36,66] The frequently-used lymphoma regimen CHOP contains cyclophosphamide, doxorubicin, vincristine, and predniso(lo)ne; in other protocols etoposide (e.g. CHOEP) or methotrexate is added.

Occasional reports indicate that cyclosporin A shows efficacy in clonal cytophagic histiocytic panniculitis and

even subcutaneous panniculitis-like T-cell lymphoma with features of HLH.[30,68] It has been suggested that cytokine release syndrome after T-cell engaging therapies can be treated with interleukin-6 blockade by tocilizumab, while the use of corticosteroids might result in a lower anti-malignancy effect of chimeric antigen receptor T cells.[34,69] However, due to the different pathogenesis of this iatrogenic condition, it is not clear whether tocilizumab will be effective as a treatment for HLH when it occurs in the context of malignancy.

Anti-viral treatment should be instituted if a treatable viral trigger is found, such as CMV or adenovirus. A beneficial impact of rituximab has been reported for some patients with EBV-driven HLH without malignancy.[70] Anti-B-cell treatment may thus be considered for HLH in the context of malignancy with EBV as a co-trigger. An additional neoplasm-directed effect may be assumed in cases of CD20-positive lymphomas. In addition to initial triggering infections, secondary infections frequently occur due to disease- and treatment-related immunosuppression. Anti-infectious prophylaxis (anti-fungal, *pneumocystis jiroveci*) and screening surveillance (aspergillus, EBV and CMV) should thus be strongly considered.

When comparing outcome data, death by HLH and death by the cancer should be ideally regarded separately. However, it is frequently impossible to differentiate between these two. The following estimators of survival have been reported for adults: a 30-day survival of the acute phase of Malignancy-Associated HLH of approximately 56%-70%, a median overall survival of 36-230 days, and a 3-year survival of 18%-55% (depending on the subtype). HLH triggered by a T-cell lymphoma has a worse prognosis than HLH occuring in the setting of a B-cell lymphoma. In a patient with lymphoma, the presence of HLH is prognostic of a poorer survival and early death.[12,15,16,65,66,71,72] It has thus been suggested that stem cell transplantation might be considered as consolidation in patients with HLH in the context of a hematologic malignancy. For pediatric patients, 56% survival following the acute phase of HLH and 36% at five years have been reported.[17]

Core Statement 10 (level of evidence 5, full consensus): In HLH During Chemotherapy:

• postponing subsequent chemotherapeutic blocks or interruption of maintenance therapy should be strongly considered, except for the event of relapse of the neoplasm;

• the necessity and extent of HLH-directed treatment depends on the clinical severity;

• infectious triggers require rigorous treatment. Anti-infectious prophylaxis (anti-fungal, *pneumocystis jiroveci*) and regular surveillance for secondary infections or reactivations (aspergillus, EBV and CMV) should be strongly considered in active HLH;

• anti-B-cell therapy may be considered in highly replicative EBV infection.

Only very limited data on the treatment of HLH During Chemotherapy are available. Since an infectious trigger is very frequent in this group, anti-infectious treatment plays a pivotal role (see previous section, including rituximab for EBV). Anti-infectious prophylaxis (anti-fungal, *pneumocystis jiroveci*) and screening surveillance (*aspergillus*, EBV and CMV) should be strongly considered. Patients with HLH During Chemotherapy are usually profoundly cytopenic and immunosuppressed. A potential positive effect of additional immunosuppression on HLH symptoms must be weighed against a possible negative effect on the treatment of the infection. Consequently, the extent and duration of HLH-directed therapy thus depends on the severity of HLH and the underlying trigger. At the lower end of intensity, consecutive blocks of chemotherapy are merely postponed or maintenance therapy is interrupted. In addition, glucocorticosteroids and immunogloublins have been administered to children and adults.[9,33,73] Whether the administration of more aggressive treatment such as etoposide is beneficial or counterproductive in this situation remains a subject of controversy.[9,35]

With regard to prognosis, adult patients with features of HLH during treatment for AML had a median overall survival of 15 months, which was significantly lower than in patients without HLH features.[9]

Summary and Conclusions

Malignancies and infections during chemotherapeutic immunosuppression are major triggering events of HLH. The tools currently being used to diagnose HLH when it occurs in the context of a malignancy are far from perfect, as the neoplasm and treatment-induced toxicities complicate interpretation of laboratory and clinical parameters. Nevertheless, heightened clinical awareness and use of the criteria available can facilitate HLH diagnosis and thus direct subsequent therapy. Given the lack of robust evidence on the optimal choice of therapeutic interventions, treatment decisions must currently be made on a case-by-case basis. It is anticipated that future prospective investigations of adults and children with Malignancy-Triggered HLH or HLH During Chemotherapy will increase understanding of the clinical and biological bases of these poorly understood, and often life-threatening, disorders.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.

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