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REVIEW

Hemophagocytic lymphohistiocytosis: Recent progress in the pathogenesis, diagnosis and treatment

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome that develops as a primary (familial/hereditary) or secondary (non-familial/hereditary) disease characterized in the majority of the cases by hereditary or acquired impaired cytotoxic T-cell (CTL) and natural killer responses. The molecular mechanisms underlying impaired immune homeostasis have been clarified, particularly for primary diseases. Familial HLH (familial hemophagocytic lymphohistiocytosis type 2-5, Chediak-Higashi syndrome, Griscelli syndrome type 2, Hermansky-Pudlak syndrome type 2) develops due to a defect in lytic granule exocytosis, impairment of (signaling lymphocytic activation molecule)-associated protein, which plays a key role in CTL activity [*e.g.*, X-linked lymphoproliferative syndrome (XLP) 1], or impairment of X-linked inhibitor of apoptosis, a potent regulator of lymphocyte homeostasis (*e.g.*, XLP2). The development of primary HLH is often triggered by infections, but not in all. Secondary HLH develops in association with infection, autoimmune diseases/rheumatological conditions and malignancy. The molecular mechanisms involved in secondary HLH cases remain unknown and the pathophysiology is not the same as primary HLH. For either primary or secondary HLH cases, immunosuppressive therapy should be given to control the hypercytokinemia with steroids, cyclosporine A, or intravenous immune globulin, and if primary HLH is diagnosed, immunochemotherapy with a regimen containing etoposide or anti-thymocyte globulin should be started. Thereafter, allogeneic hematopoietic stem-cell transplantation is recommended for primary HLH or secondary refractory disease (especially EBV-HLH).

Key words: Alemtuzumab; Anti-thymocyte globulin; Cyclosporine A; Epstein-Barr virus; Etoposide; Hematopoietic stem-cell transplantation; Hemophagocytic lymphohistiocytosis; Hereditary diseases; Immunochemotherapy; Intravenous immunoglobulin; Molecular diagnosis; Rituximab; Steroids

Core tip: This review discusses the diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH), the algorithms used to identify the underlying immune defects at the molecular level, and the optimal therapeutic approaches. For any HLH cases, a screening for primary HLH should be made following the diagnostic algorithm. During the process, immunosuppressive therapy should be started to control the hypercytokinemia with steroids, cyclosporine A, or intravenous immune globulin, and if primary HLH is confirmed, immunochemotherapy with a regimen containing etoposide or anti-thymocyte globulin should be given. Supportive measures to control hemorrhage/organ dysfunction are also required. In cases of primary HLH or secondary/refractory HLH, timely allogeneic hematopoietic stem cell transplantation is recommended.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a primary (familial/hereditary) or secondary (non-familial/hereditary) hyperinflammatory and hypercytokinemic syndrome[1,2]. Immune homeostasis is maintained by regulating the proliferation and apoptosis of activated lymphocytes and their associated granule-dependent cytotoxic activity, which plays a critical role in defense against tumor cells and cells infected with viruses[3]. The hypercytokinemia conditions associated with HLH are caused by cytokine releases from activated T cells and macrophages as a result of impaired activation-induced cell death due to uncontrolled immune responses resulting from the impaired ability of cytotoxic T-cell (CTL) and natural killer (NK) cells to kill their target cells[4-6]. Thus, marked activation of macrophages occurs, which results in hypercytokinemia. Previous reviews of primary HLH identified a hereditary impairment in the molecules involved in the multistep processes of cytolysis (from cell activation to the release of perforin and granzymes)[7,8]. Indeed, primary HLH is caused by loss-of-function mutations in the genes encoding perforin and various molecules involved in the transport, fusion and exocytosis of secretory vesicles[4-8]. In other forms of HLH, particularly Epstein-Barr virus (EBV)-driven primary HLH, deficiency in SAP (which is important for CTL function) is responsible for the marked reduction in CTL and NK cell activity; however, in XIAP (which is important for apoptosis), CTL and NK cell activity are not altered[9-11]. Secondary HLH develops in apparently immunocompetent subjects; however, some of these subjects show acquired functional reductions in CTL and NK cell activity, which are associated with viral, bacterial or parasite infections, metabolic diseases, autoimmune diseases/rheumatological conditions (termed as macrophage activation syndrome; MAS), or malignancy[12-19]. Initial diagnostic work-up in the diagnosis of HLH includes the detection of the expansion of $CD8^+$ T cell subset in the peripheral blood[20,21] and the identification of the factors that trigger the development of HLH, particularly infectious agents[22,23]. In addition, for all HLH cases, molecular screening must be performed to determine whether the disease is primary or secondary[6,24,25]. The assay of NK or CTL activity[26,27] and flow cytometric analysis of molecules, such as perforin, Munc 13-4, SAP/XIAP, is essential for rapid diagnosis[6,24,25,28] (Figure 1). Age-related factors were emphasized in the past because primary HLH usually develops during the first 3 years of life; however, more recently, late-onset cases have been identified[29-33]. The diversity of clinical features associated with primary HLH has been examined using detailed genotype-phenotype analysis methods. Among infectious agents, EBV plays a major role in cases of infection-associated primary or secondary HLH. Thus, quantification of cell-free or peripheral mononuclear cell EBV-DNA levels is extremely useful for the diagnosis of EBV-HLH and chronic active EBV infection (CAEBV)-related HLH[34-36]. The HLH-94 or HLH-2004 regimens employed in many centers has led to a significant improvement in the therapeutic results due to the efficacy of a combination of immunochemotherapy and allogeneic HSCT for treating primary and secondary HLH, especially for refractory EBV-HLH[37-39]; however, the diversity of the clinical features associated with primary HLH raises questions regarding the appropriate timing of HSCT[40-48].

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Clinical features

The initial symptoms of HLH include persistent fever, hepatic and/or renal dysfunction, splenomegaly, hemorrhagic diathesis, neurological symptoms, and other features, caused by hyperinflammatory conditions[1,2,38,49-52]. The clinical features of primary and secondary cases are not significantly different; however, some types of primary HLH are associated with hypogammaglobulinemia-related symptoms (*e.g.*, FHL5 and XLP1)[45,53], enteropathy and renal tubular dysfunction due to the epithelial abnormalities in FHL5[54] and oculocutaneous albinism in patients with Griscelli syndrome type 2 (GS-2), Chediak-Higashi syndrome (CHS), and Hermansky-Pudlak syndrome type 2 (HPS-II)[55-59], although occurrence of HLH in HPS-II deficiency is limited to a single case[58]. The most ominous findings in cases of HLH are central nervous system (CNS) disease[60-62] or an association with primary or therapy-related hematological malignancies[63-65]. The HLH conditions do not show the same severity, which is determined by the type of NK deficiency[26,27] in association with the type of genetic mutations in the primary HLH[42-48], or the degree of lymphoproliferation as represented by serum soluble IL-2R levels in the secondary HLH[66]. HLH occurs in all age groups, from premature infants and neonates to the elderly, but the majority of primary HLH cases occur in early infancy. For cases occurring during the fetal and neonatal periods[67,68], pre- or post-natal molecular diagnosis is essential[69]. Primary HLH can also develop in adolescents and adults[29-33]. Thus, especially in this older age group, a molecular diagnosis is recommended to enable a definite diagnosis of primary or secondary HLH.

Triggers and underlying diseases

The most common "trigger" for HLH is infectious disease. Viral and other types of infection cause secondary HLH[13,14,22,23,49,50]. Among them, EBV-HLH and CAEBV-related HLH, which are defined by the specific diagnostic criteria[34-36], are the most common form of secondary HLH; however, infection-induced HLH also occurs in individuals with primary HLH, MAS, and malignancy. Post-organ transplant-HLH, or post-HSCT-HLH, is a distinct subtype of secondary HLH that was described recently[70-72]. Among the various malignancies, lymphoma-associated HLH (LAHS) is the most common[73-75]. Progress in molecular diagnostic techniques

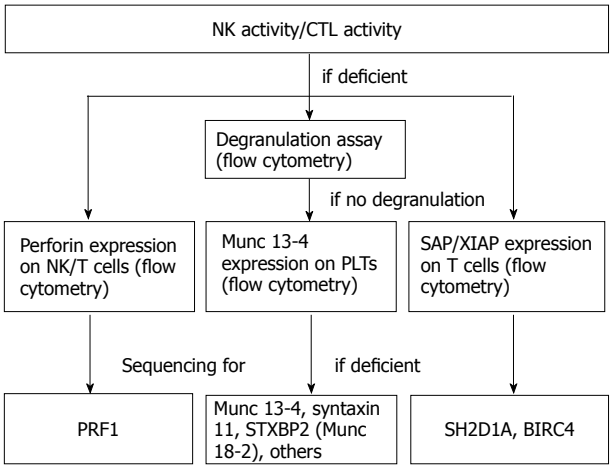

Figure 1 Diagnostic work up algorithm for a patient with primary hemophagocytic lymphohistiocytosis (familial hemophagocytic lymphohistiocytosis and X-linked lymphoproliferative syndrome)[6,22,23]. Degranulation assay is useful for familial hemophagocytic lymphohistiocytosis (FHL) type 3-5. It is advised to perform flow cytometry of peripheral blood mononuclear cells to detect the expansion of CD8+ T cells as first step of diagnosing hemophagocytic lymphohistiocytosis (HLH) prior to the work up algorism.

has led to the identification of molecular abnormality of primary HLH in cases of secondary HLH[76,77] as well as in hematological malignancies[63,64,78-80]. In addition, genotype-phenotype correlations have been identified in patients with primary HLH, particularly those associated with FHL2, FHL3, and FHL5[42-46] and with XLP[53,81-83]. It is these types of studies that identified the existence of atypical late-developing primary HLH cases in adolescents and adults[29-33], and the identification of which raises questions about how promptly HSCT should be introduced.

Laboratory findings and immunopathological features

The cardinal laboratory features associated with HLH include bicytopenia, high levels of serum ferritin, triglyceride, transaminases, lactate dehydrogenase and soluble IL-2R. Serum creatinine and BUN levels are often elevated, while plasma fibrinogen is decreased. Deficient NK activity has generally been noted[12,14-17,26,27]. Hemophagocytosis is observed on bone marrow smears or in lymph node or liver biopsies; however, the detection of hemophagocytes is not mandatory for the diagnosis. Although detection of abnormal karyotypes in bone marrow cells is rare in patients with HLH, they are occasionally detectable in cases of EBV-HLH, correlated with CAEBV[84]. Immunopathological features in HLH are characterized by uncontrolled activation of T cells, especially a significant increase in the subpopulation of CD8+ T cells with clonal expansion[20,21] and macrophages in association with overproduction of various cytokines[85,86].

Molecular genetics

The molecular defects associated with primary HLH are listed in Table 1. Molecular abnormalities have been identified in the perforin-granzyme cytotoxic molecule pathway (in FHL type 2-5, GS-2, CHS, HPS-Ⅱ), T-cell activation pathway (in XLP1), the apoptotic pathway (in XLP2), and the inducible T-cell kinase pathway (in ITK deficiency)[11,87-100]. More recently, CD27 deficiency[101,102] and magnesium transporter 1 (MAGT1) deficiency, also termed as XMEN (X-linked immunodeficiency with Mg^{2+} defect, EBV infection and neoplasm)[103], were identified. These EBV-driven ITK, or CD27 deficiency and XMEN give rise to EBV- associated lymphoproliferative disease (LPD), but does not primarily predispose to HLH; although hemophagocytosis was described in some of the cases[100,102]. These novel discoveries are expected to help elucidate the molecular mechanisms causing the inherited forms of EBV-LPD and HLH.

Table 1 List of primary hemophagocytic lymphohistiocytosis

Disease	Molecular abnormalities (chromosome location)
CTL molecule dysfunction	
Pore formation	
FHL2	Perforin (10q21-2)
Vesicle priming fusion	
FHL3	Munc13-4/Unc 13D (17q25)
FHL4	Syntaxin 11 (6q24)
FHL5	STXBP2/Munc18-2 (19p13)
Vesicle docking/trafficking	
Chediak-Higashi syndrome	LYST (1q42.1-42.2)
Griscelli syndrome, type 2	Rab27a (15q21)
Hermansky-Pudlak syndrome Ⅱ	AP-3 (3q24)
EBV-driven	
XLP1	SAP/SH2D1A (Xq25)
XLP2 (XIAP)	BIRC4 (Xq24-25)
ITK deficiency[1]	ITK (5q34)
CD27 deficiency[1]	CD27 (12p13)
XMEN[1]	MAGT1 (Xq21.1)

[1]Major clinical features in these diseases are not hemophagocytic lymphohistiocytosis (HLH) but Epstein-Barr virus (EBV)-associated lymphoproliferative disease. FHL: Familial hemophagocytic lymphohistiocytosis; XLP: X-linked lymphoproliferative disease; ITK: IL-2-inducible T cell kinase; XMEN: X-linked immunodeficiency with Mg^{2+} defect, EBV infection and neoplasia; MAGT1: Magnesium transporter 1, LYST is also called CHS1 gene. Association of hemophagocytosis was described in some cases.

Diagnosis and differential diagnosis

Achieving the definitive diagnosis of HLH is often challenging[104,105]. Currently, HLH is diagnosed according to globally accepted diagnostic criteria shown in Table 2[38]. Differential diagnoses include fulminant hepatitis or acute hepatic failure[106], severe sepsis, systemic inflammatory response syndrome, and other hyperinflammatory conditions[107]. In the differentiation of primary and secondary HLH, screening measures are employed, which include NK and CTL activity determination, degranulation assays as well as flow cytometric assay of the expression of perforin and other molecules (Figure 1)[6,24-27]. More recently, Western blot analysis was found to be useful to screen for primary HLH by detecting FHL-related proteins in platelets[28]. An accurate diagnosis is made by performing mutation analysis of the genes

Table 2 Diagnostic guidelines for hemophagocytic lymphohistiocytosis[38]

The diagnosis of HLH can be established if one of either (1) or (2) below is fulfilled	
(1) A molecular diagnosis consistent with HLH	
(2) Clinical diagnostic criteria fulfilled for 5 out of the 8 criteria below	
Clinical criteria	1 fever
	2 splenomegaly
Routine laboratory criteria	3 bicytopenia (Hb < 90 g/L, platelets < 100×10^9/L, neutrophils < 1.0×10^9/L)
	4 Hypertriglyceridemia (> 3.0 mmol/L) and/or hypofibrinogenemia (< 1.5 g/L)
Specific histopathological/marker criteria	5 hemophagocytosis
	6 low or absent NK cell activity
	7 hyperferritinemia (> 500 μg/L)
	8 hyper-sIL-2R-nemia (> 2400 U/mL)

HLH: Hemophagocytic lymphohistiocytosis; NK: Natural killer.

responsible for these hereditary diseases. EBV-HLH is diagnosed using a combination of HLH diagnostic criteria and EBV-specific data (*i.e.*, the number of EBV-DNA copies and antibody expression patterns in the serum)[34-36]. Although the majority of EBV-HLH cases in Asia are thought to be secondary HLH, molecular and genetic analyses need to be performed to determine whether they are in fact primary HLH, particularly in patients with refractory EBV-HLH[6,44,81-83,99-103]. In Europe, some patients with FHL3 or FHL5 presented with clinical features suggestive of CAEBV-related HLH[44]. Also, since the risk of malignancy is high in the condition of CTL dysfunction, patients presenting with hematological malignancies could be searched for primary HLH-related gene mutations[78-80].

Prognostic factors and clinical outcome

The ultimate treatment goal of HLH is to have disease-free survival without CNS sequelae and treatment-related acute myeloid leukemia (t-AML). The outcome of HLH depends on the severity of clinical features at the onset and types of HLH (primary or secondary). In particular, primary HLH, refractory EBV-HLH and LAHS without treatment have a poor outcome. In principle, primary HLH cases are fatal if HSCT is not performed[108]. In refractory secondary HLH, immunotherapy may not be curative, when the patients require both salvage chemotherapy and HSCT (Figure 2). Preferably, it is essential to perform HSCT before the development of CNS disease or of t-AML. In the prognostic analysis of HLH, it was found that after initial treatment, death during the acute phase occurs in 10%-15% of patients, usually due to life-threatening infections, hemorrhage, and/or irreversible organ dysfunction[37,109,110]. Death at the later stages of treatment is often due to reactivation of the disease and adverse effects associated with HSCT[109,110]. These data indicate the requirement of improved outcome of HSCT in the treatment of HLH. Although late onset cases of primary HLH are believed to carry a better prognosis, there is a report that adolescents and young adults with HLH who undergo allogeneic HSCT are at increased risk of mortality compared to younger patients[111]. The factors suggestive of a poor prognosis for those with EBV-HLH are summarized in Table 3.

Table 3 Poor prognostic factors in Epstein-Barr virus-hemophagocytic lymphohistiocytosis[34]

Persistent increase of cell-free EBV genome copies
Chromosome abnormality
Correlation with chronic active EBV infection (CAEBV)[1]
In association with primary HLH
Severe organ dysfunction, such as renal failure, CNS hemorrhage
Choice of treatment, such as timing of etoposide use, HSCT

[1]CAEBV is often associated with 1 and 2 of the above. CNS: Central nervous system; HSCT: Hematopoietic stem cell transplantation; EBV: Epstein-Barr virus; HLH: Hemophagocytic lymphohistiocytosis.

TREATMENT OF HLH

General considerations and supportive therapy

Any patients with HLH can be treated first with immunosuppressive regimens designed to control the hypercytokinemia and hyperinflammation. Such treatments include steroids (prednisolone or dexamethasone), cyclosporine A (CSA), or intravenous immune globulin (IVIG). During the initial period of therapy, finding out the triggering factors and underlying diseases as well as molecular diagnostic analyses are recommended to determine familial or non-familial diseases (Figure 1). If confirmed, primary HLH is similarly treatable with HLH-directed immunochemotherapy[6,37-41,112-116]. On the other hand, if apparent infection-triggered HLH is confirmed, rigorous treatment of any identified infectious agents is important. For any secondary HLH, application of treatment should aim to target the underlying diseases. Patients with very severe cases of HLH requiring hemodynamic and respiratory support are treated in the intensive care unit. Inotropic agents are life-saving for those that are hemodynamically unstable[117,118]. Antibacterial or antifungal agents are also required to treat opportunistic infections due to HLH-related neutropenia. Because severe thrombocytopenia and coagulopathy are both life-threatening conditions, the patient may require infusions of concentrated platelets, fresh frozen plasma, fibrinogen, and recombinant thrombomodulin[49,51,119]. Although there is no definite consensus on its benefit, plasma exchange or exchange transfusion may be used to treat the hypercytokinemia and reduce the hemorrhagic tendency during the initial treatment phase[120,121]. The addition of acyclovir to the therapeutic regimen for those with EBV-HLH is not thought to be beneficial because there is no objective evidence showing a clinical improvement using this drug[122]. However, acyclovir is useful for treating neonatal herpes simplex virus (HSV)-HLH in infancy[49,123,124]. Indeed, a combination of high-dose acyclovir, steroid pulse therapy, IVIG, and blood

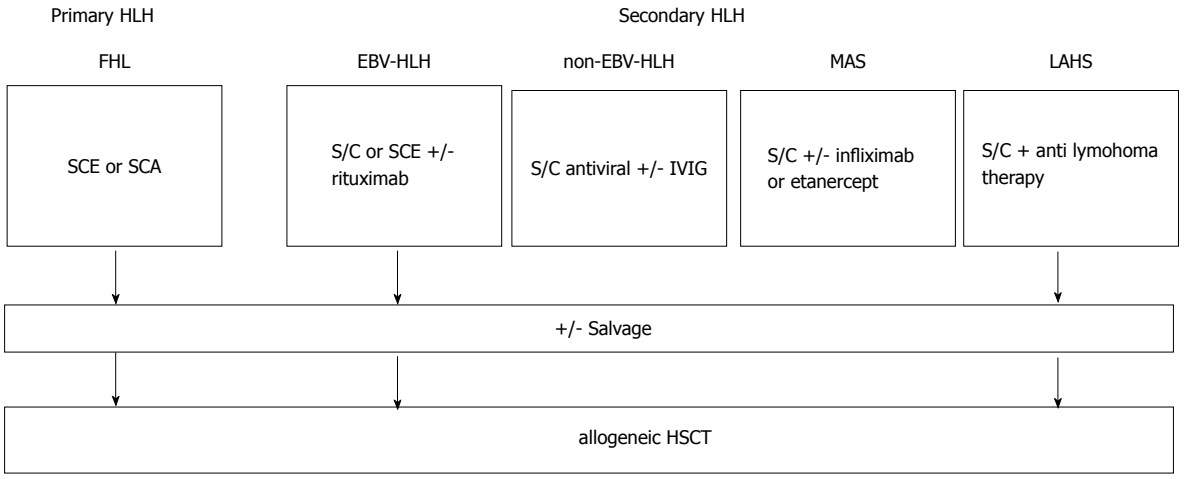

Figure 2 Flow chart illustrates the treatment pathways in hemophagocytic lymphohistiocytosis. Hematopoietic stem cell transplantation (HSCT) is required for the majority of primary hemophagocytic lymphohistiocytosis (HLH) and some of LAHS and EBV-HLH. FHL: Familial hemophagocytic lymphohistiocytosis; MAS: Macrophage activation syndrome; LAHS: Lymphoma-associated HLH; SCE: Steroids + cyclosporine A + etoposide; SCA: Steroids + cyclosporine A + ATG; IVIG: Intravenous immune globulin; S/C: Steroids alone or cyclosporine A alone or two drug combination.

transfusion has proved successful for treating neonatal HSV-HLH[125]. In patients with mycobacterium tuberculosis-associated HLH, early diagnostic confirmation and the timely administration of antituberculous medication is crucial for an improved outcome[126]. For patients with leishmania-related HLH, amphotericin B was shown to be effective[127]; however, for those with human immunodeficiency virus-related HLH, outcome remains poor even in the era of highly active antiretroviral therapy[128].

The efficacy of intrathecal chemotherapy for treating CNS disease in HLH patients has not been sufficiently evaluated. At present, the outcome for HLH patients with CNS disease is poor, even when treated with a combination of systemic immunochemotherapy and intrathecal chemotherapy[60-62]. The HLH-94 study tested the ability of a high systemic dose of dexamethasone to prevent the development of CNS disease. In addition, the study examined the use of intrathecal methotrexate in patients showing neurological symptoms at the time of disease onset; however, neither treatment appeared to prevent the exacerbation of CNS disease[37,62]. Data show that at the time of HLH diagnosis, neurological symptoms were already present in 37% of patients, and abnormal findings regarding the CSF were made in 52%; in all, 63% of patients had either neurological symptoms or abnormal CSF findings. CNS sequelae were more common in the latter group and, consistent with this, a substantial proportion of HLH survivors suffer neurological sequelae. Thus, early diagnosis of HLH and an evaluation of the CNS status including the CSF, coupled with early systemic HLH therapy, is crucial; in addition, the timely use of HSCT should be considered if reactivation of HLH with or without CNS disease is suspected to develop or to be exacerbated during the treatment[37,62,129]. However, since childhood survivors of HLH even after HSCT are shown to be at risk of long-term cognitive and psychosocial difficulties[130], prospective and systematic long-term follow-up of neurological function in these post-HSCT patients is essential.

Suppression of inflammation

In the past, IVIG was used to treat various types of HLH[49,131,132]; however, this form of treatment seems best suited to enterovirus-, hepatitis-, cytomegalovirus-, or bacteria-associated HLH[133-137]. Combined treatment with antibiotics and IVIG resulted in the full recovery of a patient with Group G streptococcal endocarditis-associated HLH[138]. Treatment with steroids alone can be effective for some HLH cases[139]. CSA quickly and efficiently suppresses the cytokines secreted by dysregulated T-cells and activated macrophages; indeed, CSA is able to control various cytokine-related pathological conditions[140,141]. Currently, the majority of HLH cases are treated first with a combination of steroids and CSA[49,140-142]. The prompt and continuous infusion of CSA (1-3 mg/kg per day over several days) is required to alleviate the cytokine "storm" as quickly as possible in patients with severe HLH, but without renal failure[49]. In addition, CSA treatment effectively supports neutrophil recovery especially in severely neutropenic Asian EBV-HLH patients during the acute phase[143].

Combined immunotherapy or immunochemotherapy

The etoposide/steroid/CSA triple combination was used in the HLH-94 or HLH-2004 regimen, consisting of 8 wk of initial therapy followed by continuation therapy and allogeneic HSCT if required. This regimen is now used in many centers to treat HLH, which comprises of dexamethasone (starting dose, 10 mg/d, Ⅳ or PO, followed by tapering), CSA (dose adjusted to obtain trough levels of 200 μg/L, PO, daily), and etoposide (150 mg/m^2, Ⅳ; a total of 10 doses during the initial 8 wk). This regimen has considerably improved the outcome for HLH patients: in the initial analysis comprising 113 patients, the 3-year survival rate was 45% (± 10%)[37]. The CNS outcomes in the patients treated with this regimen

were published in 2008[62]. Long-term follow-up results for 227 patients were published in 2011, where the estimated 5-year survival rate was 54% ± 6%, and the 5-year survival rate for 124 patients who received HSCT was 66% ± 8%[109]. The same group also suggested that this regimen should be revised as HLH-2004[58]; however, the therapeutic results of HLH-2004 have not yet been published. The HLH-94 regimen was also found to be effective when used to treat secondary EBV-HLH[144-146]. On the other hand, along the usage of HLH-94-type HLH treatment, several cases of t-AML were reported[65]. A French group used an ATG/steroid/CSA combination to treat patients with primary HLH[116,147,148], and similar to the etoposide/steroid/CSA regimen, this combination was also followed by HSCT. The effectiveness of this treatment was first described in 1993[147], where the regimen comprised steroids (2-5 mg/kg per day methylprednisolone, Ⅳ, followed by tapering), rabbit ATG (5-10 mg/kg per day for 5 d), and CSA (4-6 mg/kg per day, PO, daily). The study results were published in 2007[148]. In 38 consecutive patients with use of 45 courses of ATG, this regimen resulted in a rapid and complete response in 73%, a partial response in 24%, and no response in only one patient. Subsequent HSCT, when performed early after a complete or partial response, led to a high cure rate of 16 out of 19 cases. Overall, 21 of the 38 patients survived and there were four toxicity-related deaths. The same group also published the HSCT results for 48 patients in 2006[116]. Unfortunately, no direct comparison is possible between the therapeutic results performed after the ATG-regimen or after the HLH-94-type regimen. A regimen comprising HIT (hybrid immunotherapy)-HLH, which uses a combination of ATG/etoposide in the initial treatment phase, is currently being tested (unpublished; Jordan M, Histiocyte Society Clinical Studies 2013).

Other treatments

Rituximab is an effective treatment for some cases of EBV-HLH and has been used as a form of pre-emptive B-cell-directed therapy in patients with XLP1-related EBV-HLH or other severe forms of EBV-HLH in which EBV resides within B cells[149-152]. More recently, Chellapandian *et al*[153] examined 42 EBV-HLH cases and found that a combination of rituximab and conventional immunochemotherapy improved patient symptoms and reduced both the viral load and the level of inflammation. In the past, rituximab was thought to be unsuitable as a treatment for Asian patients with EBV-HLH in which EBV resides in T-cells or NK cells; however, the inclusion of rituximab in the initial treatment regimen may be useful in such cases[154]. R-CHOP (a combination of rituximab, doxorubicin, vincristine, cyclophosphamide and prednisolone) as well as R-etoposide are an effective combination for treating EBV-LPD-associated HLH[152]. The combination of rituximab and CSA induced remission in one patient with EBV-HLH occurring in association with CHS[57]. In addition, intrathecal rituximab is an effective treatment for post-transplant EBV-positive CNS lesions[155,156]. Alemtuzumab is effective as a bridge to allogeneic HSCT in primary HLH patients undergoing salvage treatment[157]. Marsh *et al*[158] reported that of 22 patients who received alemtuzumab (median dose, 1 mg/kg; range, 0.1-8.9 mg/kg) over a median of 4 d (range, 2-10), 64% experienced a partial response within 2 weeks. Indeed, 77% survived and underwent allogeneic HSCT, where the adverse events, including cytomegalovirus and adenovirus viremia, were reported to be "acceptable". Alemtuzumab has also been used to treat refractory MAS[159]. As other biological and experimental agents, the anti-CD25 antibody (daclizumab) was successfully used in a single adult patient with HLH[160] and the anti-TNF-α antibody (infliximab/etanercept) is an effective treatment for MAS[161-165]. Because IFN-γ plays a major role in the pathogenesis of HLH, a humanized anti-IFN-γ antibody, NI-0501(NovImmune), is currently being tested as a future treatment for the disease (unpublished; Arico M, Histiocyte Society Clinical Studies 2013), based on the murine model studies[166,167]. A study in XMEN patients showed that magnesium supplementation is an effective treatment because magnesium restores decreased intracellular free Mg^{2+} levels and corrects defective expression of NK activating receptor (NKG2D), while concurrently reducing the number of EBV-infected cells *in vivo*[103].

Allogeneic hematopoietic stem cell transplantation

Patients with primary HLH and those with refractory secondary HLH are candidates for allogeneic HSCT[37-41,112-116,168]. Primary HLH cases with nonsense (disruptive) gene mutations such as premature stop codon, or sequence frameshift generally develop symptoms in early infancy, thus require early introduction of HSCT. In these cases, delayed HSCT may have a risk of reactivation of HLH, development of CNS disease or hematological malignancies. Those with missense (hypomorphic) mutations may often wait for transplantation until adolescence or young adulthood. In secondary HLH, HSCT is planned whenever the disease becomes refractory to immunochemotherapy. For HSCT, reduced intensity conditioning (RIC) rather than myeloablative conditioning (MAC) is the preferred regimen because it results in better patient survival; however, the RIC regimen may result in mixed donor chimerism during the post-transplant period[41]. Landman-Parker *et al*[169] showed that partial engraftment of donor bone marrow cells after HSCT is sufficient to obtain long-term remission in patients with primary HLH. Experimental transplantation of perforin-deficient mice showed that 10%-20% perforin-expressing cells, with either mixed hematopoietic or CD8 (+) T-cell chimerism, are sufficient to re-establish immune regulation[170]. These data suggest that stable levels of donor chimerism (> 10%) could maintain remission in the HLH patients after HSCT. Of the 40 HLH patients who underwent allogeneic HSCT between 2003 and 2009 in Cincinnati, 14 received MAC comprising busulfan, cyclophosphamide,

and ATG plus or minus etoposide, while 26 patients received RIC comprising fludarabine, melphalan, and alemtuzumab. All patients engrafted successfully, and the overall estimated 3-year survival after HSCT was 43% for those receiving MAC and 92% for those receiving RIC ($P = 0.0001$)[41]. In Japan, 57 patients (43 with primary HLH and 14 with EBV-HLH) underwent HSCT between 1995 and 2005. Data show that EBV-HLH patients had a better prognosis after HSCT than primary HLH patients, also demonstrating that the RIC-conditioning regimen significantly improves the outcome of patients undergoing allogeneic HSCT[40].

CONCLUSION

Recent progress has been reviewed on how to understand the pathogenesis, how to diagnose and how to make treatment decisions in patients with HLH. Although the outcomes have significantly improved over the past decade, further refinement of treatment is required at the initial phase of the disease as well as pre- and post HSCT periods with special care for CNS disease in order to promise a cure with excellent quality of life in these patients with HLH.

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