

REVIEW

Hemophagocytic Syndrome Associated With Hematologic Malignancies

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KEY WORDS: *hemophagocytic syndrome; lymphoma associated hemophagocytic syndrome; NK/T-cell lymphoma; B-cell lymphoma*

LIST OF ABBREVIATIONS

CMV = cytomegalovirus
CsA = cyclosporin A
CTL = cytotoxic T-lymphocytes
DIC = disseminated intravascular coagulation
DLBCL = diffuse large B-cell lymphoma
DXM = dexamethasone
EBV = Epstein-Barr virus
GCSF = granulocyte colony stimulating factor
GVHD = graft versus host disease
GVL = graft versus lymphoma
HHV = human herpesvirus
HPS = hemophagocytic syndrome
HSV = herpes simplex virus
IFN = interferon
IL = interleukin
IVIG = intravenous immunoglobulin
IPI = international prognostic index
LAHS = lymphoma associated hemophagocytic syndrome
LDH = lactic dehydrogenase
NK = natural killer
PCR = polymerase chain reaction
RIC = reduced intensity conditioning
SCT = stem cell transplantation
TIA = T-cell intercellular antigen
TNF = tumor necrosis factor
VP-16 = etoposide
VZV = varicella zoster virus

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Manuscript received February 8, 2011;
Revised manuscript received May 31,
2011; Accepted June 2, 2011

Conflict of interest: none declared

ABSTRACT

Hemophagocytic syndromes (HPS) may occur in patients of all age groups. Secondary HPS is more frequent than primary (familial) and is usually described in patients with an underlying immune disorder. This clinicopathological entity is the result of hemophagocytosis of hemopoietic cells due to activation of morphologically benign macrophages in the bone marrow. Clinical symptoms include fever, hepatosplenomegaly, severe cytopenias, dyslipidemia, and frequent coagulopathy. The prognosis is dismal. Hematologic malignancies are often involved in HPS, which may present at any disease phase. Non-Hodgkin lymphomas and less frequently Hodgkin disease have been associated with HPS. Lymphoma associated hemophagocytic syndrome (LAHS) accounts for 40-50% of HPS where an underlying condition can be defined. NK/T and T peripheral lymphomas are responsible for 80% of LAHS. As far as B-cell lymphomas are concerned, their intravascular variant usually presents with LAHS (intravascular lymphomatosis), rarely encountered in Western countries and increasingly reported in Asian countries. The pathogenesis of HPS is not fully understood, but it seems to differ between T- and B-cell lymphomas. Epstein-Barr virus is thought to have an important part in the pathogenetic process, since it has been detected both in Hodgkin and non-Hodgkin lymphomas presenting with HPS. Treatment decisions depend upon the underlying condition and its phase. However the most acceptable treatment option is currently immunochemotherapy followed by myeloablative stem cell transplantation.

INTRODUCTION

Hemophagocytic syndrome (HPS) is a clinically and pathologically well defined disease entity characterized by systemic activation of benign macrophages showing extensive phagocytosis of hematopoietic cells.¹ Acquired HPS in adults occurs in different occasions, including infections, autoimmune diseases, carcinomas and hematologic malignancies (Table 1).

Clinicopathological studies of HPS have revealed that in the majority of patients it is associated with hematological malignancies, mainly non-Hodgkin's lymphoma and rarely Hodgkin's disease.⁵ The lymphoma-associated hemophagocytic syndrome (LAHS) has been reported mostly in adults and can develop at presentation, during or after treatment, at remission, relapse or transformation. Although infection is sometimes present, a known trigger factor cannot always be identified.¹⁻³ As the clinical course of LAHS is rapidly progressive and sometimes even fatal, an ac-

TABLE 1. Classification and Underlying Conditions of Hemophagocytic Syndrome (HPS)

Primary (Genetic) HPS	
1. Familial hemophagocytic lymphohistiocytosis (FHL)	• Known gene defects (perforin, munc 13-4, syntaxin 11) • Unknown gene defects
2. Immune deficiency syndromes	• Chédiak-Higashi syndrome • Griscelli syndrome • X-linked lymphoproliferative syndrome (XLP)
Secondary (Acquired) HPS	
1. Infection-associated hemophagocytic syndrome (IAHS)	• Viruses • Bacteria • Other (fungi, leishmania)
2. Malignancy-associated hemophagocytic syndrome	• Lymphoma-associated hemophagocytic syndrome (LAHS) • Other (multiple myeloma, acute leukemia, mycosis fungoides, melanoma, hepatocellular carcinoma)
3. Autoimmune-associated hemophagocytic syndrome (macrophage activation syndrome)	
4. Immune suppression/organ transplantation	
5. Other (e.g. drug-associated)	

curate diagnosis and introduction of appropriate treatment are mandatory.²

CLINICAL SYMPTOMS AND LABORATORY FINDINGS

The clinical and biological features appear to be mainly related to HPS. They remain ill-defined because the clinical cases are rare and diagnosed with difficulty. Hemophagocytic syndrome manifestations may be masked or modified by the malignant process. According to the majority of reports, the clinical presentation is systemic with B-symptoms, prolonged fever, weight loss, hepatosplenomegaly and cytopenias, which are the cardinal symptoms of HPS. Lymphadenopathy and skin involvement are less frequent.^{2,7-11} Anemia and thrombocytopenia are the most common cytopenias (>80%), while neutropenia is less frequently observed (<50%).^{5,11}

In most cases liver function is abnormal. Laboratory findings include high levels of triglycerides, ferritin, transaminases, bilirubin and lactic dehydrogenase (LDH) and a low fibrinogen. Elevated LDH and hyperferritinemia were observed in

>90% of the patients with LAHS.^{5,11} Another valuable disease marker is the soluble interleukin-2 receptor (s CD25), whose constantly increased levels are indicative of active HPS. Furthermore, impaired or absent function of NK and cytotoxic T-cells has been reported.^{1,12} In most cases, lymphomas in patients with LAHS were high-intermediate or high risk (90%) according to the international prognostic index (IPI).⁵

The clinical presentation of disseminated intravascular coagulation (DIC) depends on the histological type of lymphoma. Specifically, DIC was observed in all patients with intravascular large B cell LAHS, in almost half of the cases of T or T/NK cell LAHS and, finally, no coagulation abnormalities were detected in the majority of other type of B cell LAHS.^{5,13-15} The serum cytokine profile of LAHS has been described. Serum levels of proinflammatory and anti-inflammatory cytokines, but not the Th2 cytokine IL-2, are elevated, thus reflecting the suggested “cytokine storm”.¹⁶

Since in most cases tumour mass is not prominent, bone marrow biopsy is usually performed because of fever, weight loss or cytopenia, and rarely as part of clinical staging of an already diagnosed lymphoma.¹⁷ Nevertheless, the main lesion within these biopsies was histiocytosis with hemophagocytosis, whereas the neoplastic lymphoid infiltrate was equivocal in most cases, requiring an immunolabeling with CD20 and CD3 antibodies for its detection.^{11,17} Bone marrow infiltration was revealed in all intravascular B-cell lymphomas and in the vast majority of T,T/NK lymphomas.^{15,11} Limited data from reported cases of Hodgkin's lymphoma and other histological type of diffuse large B-cell lymphoma (DLBCL), revealed less frequent bone marrow infiltration.^{11,18,19} Interestingly in patients with LAHS, the Epstein-Barr virus (EBV) genome was present in most patients with T/NK cell lymphoma, but was detected only rarely in patients with B-cell lymphoma.²⁰

PATHOPHYSIOLOGY

The pathogenetic mechanism of HPS remains unclear.¹ However, the majority of reports support the concept of mature, activated macrophages as the main effectors in HPS. Dendritic, natural killer (NK) cells and cytotoxic T-lymphocytes (CTLs) also play a key role in the pathogenesis HPS. These cells are normally activated by an immune stimulus and mutually trigger each other. As a result the infected cell is killed, the antigen removed and termination of the immune response occurs. Hemophagocytosis results from poorly controlled macrophage activity.¹² Although molecular defects have been identified in patients with hereditary HPS forms, this was not the case in non-hereditary HPS, including LAHS.²¹ However, depressed NK activity has been observed in such patients. Defective cytotoxic activity of NK and CTLs impairs the elimination of antigen expressing cellular targets, causing continuous immune activation, while preventing

down-regulation of the immune response. Sustained immune activation leads to the clinical presentation of HPS, through high levels of cytokines.²²⁻²⁴

It has been reported that in patients with active HPS, serum levels of interferon- γ (IFN- γ), interleukin (IL)-12 and IL-18 are significantly higher than in patients in the remission phase or in healthy controls. These findings reflect the importance of Th1 cytokines in the HPS mechanism.^{23,25} Furthermore, serum levels of the proinflammatory cytokines tumor necrosis factor (TNF)- α , IL-1 β and IL-6 are also elevated in patients with active HPS.^{23,25,26} The cytokine profile seems to be somewhat different in patients with LAHS, depending on the underlying lymphoma. Ohno et al reported much higher levels of IL-6, IL-10 and TNF- α in patients with B-LAHS compared to patients with T-LAHS, whereas the latter presented with higher levels of IFN- γ .¹⁶ These results are implicational of a difference in the pathogenesis of LAHS in B- and T- lymphomas.

Various studies have demonstrated a viral association between lymphomas and HPS. In T- and NK- cell lymphoma, infection by Epstein-Barr virus has been suggested to play a significant role in lymphomatous transformation and in macrophage activation causing LAHS.¹¹ According to emerging reports, presentation EBV-associated T/NK- cell lymphomas of particular histological types, in virus-associated hemophagocytic syndrome, indicates intimate relationship between EBV and T cells in HPS.²⁷ Lay et al showed that infection of two T-cell lines caused up-regulation of TNF- α , which in combination with IFN- γ caused activation of macrophages both in vitro and in vivo.²⁸ In some cases of B-cell lymphomas with LAHS, human herpesvirus-6 (HHV-6) infection was detected in tumour tissue by polymerase chain reaction (PCR), but it was not possible to determine whether HHV-6 infected neoplastic or reactive cells. Although serologic data for CMV, HSV, varicella zoster virus (VZV), and HHV6 rarely showed active infection, the possibility that a viral infection other than EBV could up-regulate cytokines, initiate LAHS and disappear thereafter, could not be completely excluded.^{11,29,30}

HISTOPATHOLOGICAL FINDINGS

Although lymphomas with HPS show marked heterogeneity as far as classification is concerned, they share some common clinical and biologic features that appear to be related to hemophagocytosis itself – the ingestion of cellular blood components and their precursors by macrophages.¹¹ The majority of HPS-associated lymphomas seem to involve the bone marrow at presentation. The main lesion within a bone marrow biopsy is histiocytosis with hemophagocytosis. In most cases the neoplastic lymphoid infiltrate, if present, is intermingled within normal hematopoietic cells, and rarely forms focal infiltrates.^{8,18,14}

The role of EBV in the pathogenesis of LAHS, although

not thoroughly understood, is also depicted in the histopathological findings. More than 80% of NK/T- lymphomas have been documented as EBV positive by detection of EBV encoded RNA (EBER) and/or latent membrane protein (LMP)-1 in tumour cells with in situ hybridization. Recent studies report the presence of EBV in tumour cells of B-lymphomas as well, whereas 94% of Hodgkin lymphomas presenting with LAHS were EBV positive.^{6,7,10,31,32} Cytotoxic agents such as granzyme and T-cell intercellular antigen (TIA)-1 are always present in NK/T- lymphomas. Similarly, it has been reported that in B-cell lymphomas (mainly DLBCL) with LAHS a reactive T-cell population composed by activated cytotoxic cells (TIA1 $\pm$ granzyme) is present, often outnumbering the neoplastic B-cells.^{8,13,26}

DIAGNOSIS

The diagnosis of HPS is based on both clinical and pathological findings. Diagnostic criteria for HPS were first established in 1991 by the Histiocyte Society and revised in 2004 as shown in Table 2. Other supportive evidence of HPS includes cerebral symptoms with moderate pleocytosis and/or elevated protein, transaminitis, hyperbilirubinemia, and elevated LDH.

Prolonged fever, unresponsive to antibiotics, hepatosplenomegaly and cytopenias, should alert the physician and consider the HPS in differential diagnosis. Minimal diagnostic requirements are a complete blood count, liver enzymes, bilirubin, triglycerides, ferritin and a coagulation profile including

TABLE 2. Diagnostic Criteria for the Hemophagocytic Syndrome (HPS)

1. Familial disease/known genetic defect
2. Clinical and laboratory criteria (should fulfil at least 5/8)
• Fever
• Splenomegaly
• Cytopenia = at least 2 cell lines
Hemoglobin <9 g/dL
Platelets <100 $\times$ 10 ⁹ /L
Neutrophils <1 $\times$ 10 ⁹ /L
• Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides $\geq$ 265 mg/dL
Fibrinogen <150 mg/L
• Ferritin >500 μ g/L
• Soluble CD25 $\geq$ 2400 U/ml
• Decreased or absent NK-cell activity
• Hemophagocytosis in bone marrow, spleen or lymph nodes

fibrinogen. Patients suspected of HPS should receive a bone marrow examination and lumbar puncture at an experienced center. Moreover valuable diagnostic parameters are increased concentrations of sCD25 and decreased NK cell function.

A search for an infectious organism, such as EBV, CMV, HSV, adenovirus, parvovirus B19 and leishmania is recommended, since most of these agents are treatable. In order to diagnose secondary HPS it is necessary to detect the underlying disorder. The patient should be screened for an underlying immunodeficiency, autoimmune disease and malignancies by appropriate studies. It should be kept in mind that HPS and lymphoma can be associated at initial presentation, but HPS can also precede the lymphoma or occur at any stage of treatment.

The main diagnostic problem is that, initially, HPS masquerades as a normal infection and too little attention is paid to the severity of symptoms. Much time may then be lost with extensive work-up for an infectious disease or with prolonged antibiotic treatment. In some cases, the patient's improvement with unspecific methods, such as transfusion, may be misleading. The fever may subside and laboratory values may transiently return to normal. The absence of hemaphagocytosis is often the reason why the diagnosis of HPS is ruled out.

TREATMENT

Hemophagocytic syndrome has a very dramatic course, eventually leading to multiple organ failure with high mortality. One-year overall survival without treatment has been reported 5%, while death rates even after treatment approach 60%.^{1,5,34} Prompt and definitive treatment is therefore required. Historically, patients with HPS have been treated with corticosteroids, intravenous immunoglobulin (IVIG), etoposide (VP-16), or a combination of these drugs. However, since there are still no established guidelines concerning adult HPS, and LAHS in particular, it remains difficult to determine exactly how each case should be treated. The therapeutic approach depends on the underlying condition and its phase, and the presence or not of a triggering factor, such as infection. However, the main treatment strategies consist of general measures and, more importantly, specific treatment of the underlying condition.^{1,34} The main treatment goals and approaches are shown in Table 3.

Supportive care is considered in order to avoid the risks related to cytopenias and disseminated intravascular coagulation. Administration of antibiotics and antiviral agents controls or reduces the risk of opportunistic infectious complications. Red blood cells, platelet and fresh frozen plasma transfusion should be given according to laboratory and clinical findings.³⁵ Because of the risk of clinical deterioration, administration of granulocyte colony stimulating factor (G-CSF) is not generally proposed.³⁶

TABLE 3. Treatment Goals and Approaches to Hemophagocytic Syndrome.

Immediate goals

1. Supportive care

- Infection control (antibiotics/antivirals)
- Transfusion (RBC, PLT, FFP)

2. Suppress severe hyperinflammation

- Corticosteroids (high dose dexamethasone)
- Cyclosporin A
- IVIG

3. Kill antigen-presenting cells

- Etoposide

Long-term goals: Treatment of underlying malignancy

1. Chemotherapy

- Hodgkin lymphoma: ABVD
- Non-Hodgkin lymphoma: intensive multi-agent chemotherapy

2. Autologous SCT

3. Allogeneic SCT

ABVD = andriamycin, bleomycin, vincristine, dacarbazine; FFP = fresh frozen plasma; IVIG = intravenous immunoglobulin; PLT = platelets; RBC = red blood cells; SCT = stem cell transplantation

Plasmapheresis and/or exchange transfusion, have been described in small series and case reports. Even though the results were mostly encouraging, it is still questioned whether cytokine clearance really takes place and whether this is the key mechanism.^{37,38}

Intravenous immunoglobulin (IVIG), due to its broad spectrum of mechanisms of action, can be effective in HPS treatment. IVIG inhibits complement activation, down regulates T/B cell functions, neutralises superantigens and infectious agents, neutralises cytokines and enhances clearance of pathogenetic antibodies. IVIG may be administered alone or in combination with other agents. Although IVIG was generally well tolerated and the results were relatively good, it is worth mentioning that in cases of malignancy associated HPS, sustained improvement was never actually observed.³⁹⁻⁴¹

Corticosteroids have long been thought to be one of the cornerstones of HPS treatment in the presence of a triggering factor. Life threatening hyperinflammation caused by excessive cytokines can be effectively treated, since corticosteroids are cytotoxic for lymphocytes and, therefore, inhibit cytokine expression and differentiation of dendritic cells. Water-soluble brain-penetrating corticosteroids are preferred. Some authors suggest to decrease immunosuppression especially in patients with infection, but a short course of corticosteroids seems to be justified.^{1,35,42}

Cyclosporin A (CsA), a calcineurin inhibitor, has proven to be effective in controlling various cytokine-related pathological conditions, as it affects T-lymphocyte activation, and macrophage and dendritic cell function.⁴³ It can be a key drug in HPS induction and maintenance therapy leading to reduction of hypercytokinemia. It has also been reported that introducing CsA treatment effectively supports neutrophil recovery during the acute phase of HPS in severely neutropenic patients.^{36,44-46} Its importance in LAHS treatment is implied by the fact that CsA, as single agent therapy, is effective in T-cell lymphoproliferative syndromes.^{40,41} Administration of CsA depends on an appropriate renal function, while hepatic and central nervous system side effects may mimic HPS manifestations. Moreover, there is no consensus regarding when to start and when to terminate treatment with CsA.⁴²

Etoposide (VP-16) was introduced to the treatment of HPS in the 80's. It is highly active against monocytic and histiocytic diseases. Its mode of action in HPS seems to be the killing of pathogen-infected antigen-presenting cells in order to reduce the stimulus for the ongoing but ineffective activation of cytotoxic cells. Patients with lymphoproliferative disorders and LAHS may benefit from the combination of VP-16 and CsA, since it induces apoptosis in NK/T cell lymphoma cell lines.⁵⁰ In this combination neutropenia resulting from VP-16 is attenuated by the concurrent use of CsA. Long-term low dose oral VP-16 has been suggested to be a safe and effective option.^{51,52} Even so, careful follow-up of patients treated with VP-16 is required, because VP-16 has been associated with secondary malignancies, most frequently treatment related secondary acute myeloid leukemia and myelodysplastic syndrome.⁵³

In the international HLA-94 protocol treatment consisted of an initial 8-week period of dexamethasone (DXM) and VP-16, followed by maintenance with CsA and alternating pulses of VP-16 and DXM. Currently, the most common treatment for HPS is a core combination of corticosteroids and VP-16, as suggested in the previously mentioned protocol. This therapy aims to eventually eradicate the proliferating T and NK cells, and activated macrophages, thus resolving the HPS.⁵⁰

Antithymocyte globulin, especially when combined with corticosteroids, might be equivalent to VP-16 in situations with refractory disease, but its significant side effects, i.e. allergic reactions and severe immunosuppression limit its use in clinical practice.⁴⁹ Alemtuzumab and 2CdA have also been used for HPS therapy with no definite results.

Lymphoma associated hemophagocytic syndromes are refractory or respond temporarily to immunosuppressive therapeutic approaches. In this setting, treatment of the underlying lymphoma is imperative. Intensive multi-agent chemotherapy is the treatment of choice. However, the standard regimen CHOP, consisting of andriamycin, cyclophosphamide, vincristine and prednisone, is not effective enough in more than 70% of cases with NHL associated with HPS. Most patients

present a transient response and eventually relapse.⁵ Second line chemotherapy is then required preferably followed by autologous or allogeneic stem cell transplantation (SCT). Second line regimens usually include high-dose cytosine arabinoside, vincristine, VP-16, cyclophosphamide, cisplatin, and steroids. L-asparaginase based chemotherapy has proven to be effective in aggressive T/NK lymphoma, and methotrexate based regimens are a good alternative for intravascular and other B-cell lymphomas. A combination of CsA with multi-agent chemotherapy is considered to be the most effective therapy and in some cases even good enough for a cure without SCT.^{34,42,54,55}

Since only a few cases of Hodgkin's lymphoma presenting with hemophagocytic syndrome have been published, the data are rather scarce. However, these patients seem to respond better to standard therapy with ABVD (andriamycin, bleomycin, vincristine, dacarbazine). In case of relapse, second-line treatment followed by autologous or allogeneic SCT is imperative.

Myeloablative chemotherapy and subsequent SCT are currently the gold standard of treatment regimens for therapy resistant non familial HPS and LAHS. Autologous SCT has been used as part of front line therapy in patients with aggressive lymphomas, such as those associated with HPS, but its role on survival prolongation is still under investigation. The BEAM (BCNU-carmustine, etoposide, cytarabine, and melphalan) chemotherapy scheme is the most commonly used conditioning regimen. Although the results were improved compared to those after chemotherapy only, relapse rates remain relatively high and overall survival does not exceed 30% in two years.^{34,56-58}

Allogeneic SCT is theoretically preferred over autologous SCT, because the stem cell source in this case is tumour free, and the possibility of a graft versus lymphoma effect is present.⁵⁹ In 2002, Henter et al first reported the results of a prospective multicenter therapeutic trial for patients with HPS. Induction therapy consisted of combination chemo/immunotherapy to achieve remission and SCT followed in order to achieve a definitive cure. Overall, 2-year survival was reported as 55%, with most fatalities occurring either early after diagnosis or early after transplantation, mainly due to relapse or infection.⁶⁰ A busulfan/fludarabine/VP-16 based regimen is commonly used for patients with HPS, although total body irradiation-based regimens have also been employed in refractory disease. However, in cases of underlying lymphoma, a combination containing alemtuzumab may be more effective. Primary non-engraftment occurred 10-25% of patients who received myeloablative conditioning therapy. The development of secondary malignancies, i.e. myelodysplastic syndrome/acute myeloid leukemia was a major problem, but the researchers conclude that this risk is relatively limited and acceptable considering the positive therapeutic effects of the combination of chemo/immunotherapy with SCT.⁶⁰⁻⁶³

The causes of death were multifactorial, including infection, hemorrhage, organ failure and graft versus host disease

(GVHD), while the occurrence of veno-occlusive disease and interstitial pneumonia was remarkable as well. As expected, HLA-matched sibling donors were associated with higher survival rates, compared to matched unrelated donors, haploidentical and cord blood stem cells.⁵⁹ Data from these series also suggest that both SCT complications and outcomes are affected by the HPS disease status. In cases of active disease at the time of transplant overall survival was found to be decreased. Furthermore, Horne et al correlated active disease at the time of transplant with primary graft failure. They also reported that, independent of the clinical status at the time of transplantation, patients whose disease was more refractory to initial medical therapy had worse overall survival rates after SCT.^{64,65}

A reduced-intensity conditioning (RIC) regimen can reduce treatment related mortality, while the graft versus lymphoma effect is preserved. Marsh et al recently published the results of SCT after a reduced-intensity preparative regimen consisting of alemtuzumab, fludarabine, and melphalan. In this report, even though infection rates were not different compared to those of myeloablative series, no non-infectious complications were documented. However, a high incidence of mixed chimerism among the RIC patients was observed.^{61,67,68} There are conflicting data concerning the feasibility of RIC transplantation in patients with LAHS. Some studies demonstrate no preservation of graft versus lymphoma (GVL) effect after RIC-SCT in patients with aggressive lymphomas, and others show encouraging results in terms of event-free survival. Consequently, a myeloablative regimen should be the standard of care for the time being.

Overall, with regard to the therapeutic approach, prompt and effective therapy is imperative. It is not an easy decision to treat a febrile and pancytopenic patient with aggressive immuno/chemotherapy. However, if hyperinflammation is not controlled, the patient will definitely succumb to infection or multiple organ failure.

CONCLUSION

In patients with prolonged fever, unresponsive to antibiotics, marked cytopenias, coagulopathy and hepatosplenomegaly, the differential diagnosis of HPS should be considered. The most common cause of acquired HPS is LAHS, most cases being associated with T-cell or NK/T-cell lymphoma. The pathogenetic procedure leading to this condition remains unclear, but it has been demonstrated that LAHS is highly aggressive, having only transient response to comprehensive therapy and very dismal prognosis. Consequently, rapid therapeutic decisions need to be made. In absence of specific guidelines for the treatment of patients with LAHS, immuno/chemotherapy followed by autologous or allogeneic SCT is considered to be the preferred approach.

REFERENCES

1. Janka G. Hemophagocytic syndromes. *Blood Rev* 2007;21: 245-253.
2. Jaffe ES, Costa J, Fauci AS, et al. Malignant lymphoma and erythrophagocytosis stimulating histiocytosis. *Am J Med* 1983; 75: 741-749.
3. Falini B, Pileri S, De Solas I, et al. Peripheral T-cell lymphoma, associated with hemophagocytic syndrome. *Blood* 1990; 75: 434-444.
4. Quintanilla-Martinez L, Kumar S, Fend F, et al. Fulminant EBV(+) T-cell lymphoproliferative disorder following acute/chronic EBV infection: a distinct clinicopathologic syndrome. *Blood* 2000;96: 443-451.
5. Han AR, Lee HR, Park BB, et al. Lymphoma-associated hemophagocytic syndrome: clinical features and treatment outcome. *Ann Hematol* 2007; 86: 493-498.
6. Kajima H, Takei N, Mukai HY, et al. Hemophagocytic syndrome as the primary clinical symptom of Hodgkin's disease. *Ann Hematol* 2003; 82: 53-56.
7. Ohshima K, Suzumiya J, Suginora M, et al. Clinicopathological study of severe chronic active Epstein-Barr virus infection that developed in association with lymphoproliferative disorder and/or hemophagocytic syndrome. *Pathol Int* 1998; 48: 934-943.
8. Shimazaki C, Inaba T, Shimura K, et al. B-cell lymphoma associated with hemophagocytic syndrome: a clinical, immunological and cytogenetic study. *Br J Haematol* 1999; 104: 672-679.
9. Tiab M, Mechinaud F, Hamidou M, Gaillard F, Raffi F, Harousseau JL. Hemophagocytic syndrome: a series of 23 cases. *Ann Med Interne (Paris)* 1996;147:138-144.
10. Yao M, Cheng AI, Su IJ, et al. Clinicopathological spectrum of hemophagocytic syndrome in Epstein-Barr virus-associated peripheral T-cell lymphoma. *Br J Haematol* 1994;87:535-543.
11. Allory Y, Challine D, Haioun C, et al. Bone marrow involvement in lymphomas with hemophagocytic syndrome at presentation. *Am J Surg Pathol* 2001;25:865-874.
12. Schneider EM, Lorenz I, Muller-Rosenberger M, et al. Hemophagocytic lymphohistiocytosis is associated with deficiencies of cellular cytolysis but normal expression of transcripts relevant to killer-induced apoptosis. *Blood* 2002; 100: 2891-2898.
13. Miyahara M, Sano M, Shibata K, et al. B-cell lymphoma associated hemophagocytic syndrome: clinicopathological characteristics. *Ann Hematol* 2000; 79: 378-388.
14. Murase T, Nakemura S, Tashiro K, et al. Malignant histiocytosis-like B-cell lymphoma, a distinct pathologic variant of intravascular lymphomatosis: a report of five cases and review of the literature. *Br J Haematol* 1997; 99: 656-664.
15. Murase T, Yamaguchi M, Suzuki R, et al. Intravascular large B-cell lymphoma (IVBCL): a clinicopathologic study of 96 cases with special reference of the immunophenotype heterogeneity of CD5. *Blood* 2007; 109: 478-485.
16. Ohno T, Ueda Y, Nagai K, et al. The serum cytokine profiles of lymphoma-associated hemophagocytic syndrome: A comparative analysis of B-cell and T-cell/Natural killer cell lymphomas. *Int J Hematol* 2002;77:286-294.

17. Takeshita M, Kikuchi M, Ohshima K, et al. Bone marrow findings in malignant histiocytosis and/or malignant lymphoma with concurrent hemophagocytic syndrome. *Leuk Lymphoma* 1993; 12: 79-89.
18. Menard F, Bessin C, Rince P, et al. Hodgkin lymphoma-associated hemophagocytic syndrome: A disorder strongly correlated with Epstein-Barr Virus. *Clin Infect Dis* 2008; 47: 531-534.
19. Choi Y, Park J, Kim S, et al. Aggressive NK-cell leukaemia associated with reactive haemophagocytic syndrome. *Clin Dermatol* 2005; 31: 83-85.
20. Takahashi N, Chubachi A, Miura I, et al. Lymphoma associated hemophagocytic syndrome in Japan. *Rinsho Ketsueki* 1999; 40: 542-549.
21. Filipovich A. Hemophagocytic lymphohistiocytosis (HLH) and related disorders *Hematology Am Soc Hematol Educ Program* 2009; pp. 127-132.
22. Henter J, Elinder G, Sober O, et al. Hypercytokinemia in familial hemophagocytic lymphohistiocytosis. *Blood* 1991;78:2918-2922.
23. Osugi Y, Hara J, Tagawa S, et al. Cytokine production regulating Th1 and Th2 cytokines in hemophagocytic lymphohistiocytosis. *Blood* 1997;89:4100-4103.
24. Larroche C, Mouthon L. Pathogenesis of hemophagocytic syndrome (HPS). *Autoimmun Rev* 2004;3:69-75.
25. Takada H, Nomura A, Ohga S, et al. Interleukin-18 in hemophagocytic lymphohistiocytosis. *Leuk Lymphoma* 2001; 42:21-28.
26. Imashuku S, Hibi S, Sako M, et al. Soluble interleukin-2 receptor: a useful prognostic factor for patients with hemophagocytic lymphohistiocytosis. *Blood* 1995; 86:4706-4707.
27. Chuang C, Lay J, Hsieh W, Su I. Pathogenesis and mechanism of disease progression from hemophagocytic lymphohistiocytosis to Epstein-Barr virus-associated T-cell lymphoma: Nuclear factor- κ B pathway as a potential therapeutic target. *Cancer Sci* 2007;98:1281-1287.
28. Lay J, Tsao C, Chen J, et al. Upregulation of tumor necrosis factor- α gene by Epstein-Barr virus-infected T-cells in the pathogenesis of hemophagocytic syndrome. *J Clin Invest* 1997;100:1969-1979.
29. Hasselbom S, Linde A, Ridell B. Hodgkin's lymphoma, Epstein-Barr virus reactivation and fatal haemophagocytic syndrome. *J Intern Med* 2004; 255: 289-295.
30. Ohno T, Miyake N, Hada S. Hemophagocytic syndrome in five patients with Epstein-Barr virus negative B-cell lymphoma *Cancer* 1998; 82:1963 - 72.
31. Ohshima K, Haraoka S, Harada N, et al. Hepatosplenic gamma delta T-cell lymphoma: relation to Epstein-Barr virus infection and activated cytotoxic molecules. *Histopathology* 2000;36:127-135.
32. Su I, Hsu Y, Lin M, et al. Epstein-Barr virus-containing T-cell lymphoma presents with hemophagocytic syndrome mimicking malignant histiocytosis. *Cancer* 1993;72:2019-2027.
33. Chuang H, Lay J, Hsieh W, et al. Epstein-Barr virus LMP1 inhibits the expression of SAP gene and upregulates Th1 cytokines in the pathogenesis of hemophagocytic syndrome. *Blood* 2005;106:3090-3096.
34. Imashuru S. Advances in the management of hemophagocytic lymphocytosis. *Int J Hematol* 2000;72:1-11.
35. Emmenegger U, Schaer D, Larroche C, Neftel K. Haemophagocytic syndromes in adults: current concepts and challenges ahead. *Swiss Med Wkly* 225;135:299-314.
36. Quesnel B, Catteau B, Aznar V, et al. Successful treatment of juvenile rheumatoid arthritis associated haemophagocytic syndrome by cyclosporin A with transient exacerbation by conventional-dose G-CSF. *Br J Haematol* 1997;97:508-510.
37. Goto H, Matsuo H, Nakane S, et al. Plasmapheresis affects T helper type-1/T helper type-2 balance of circulating peripheral lymphocytes. *Ther Apher* 2001;5:494-496.
38. Satomi A, Nagai S, Nagai T, et al. Effect of plasma exchange on refractory hemophagocytic syndrome complicated with myelodysplastic syndrome. *Ther Apher* 1999;3:317-319.
39. Gill DS, Spencer A, Cobcroft RG. High-dose gamma-globulin therapy in the reactive haemophagocytic syndrome. *Br J Haematol* 1994;88:204-206.
40. Freeman B, Rathore MH, Salman E, et al. Intravenously administered immune globulin for the treatment of infection-associated haemophagocytic syndrome. *J Pediatr* 1993;123:479-481.
41. Nagasawa M, Okawa H, Yata J. Deleterious effects of high dose g-globulin therapy on patients with hemophagocytic syndrome. *Int J Hematol* 1994;60:91-93.
42. Imashuku S, Hibi S, Ohara T, et al. Effective control of Epstein-Barr virus-related hemophagocytic lymphohistiocytosis with immuno-chemotherapy. *Blood* 1999;93:1869-1874.
43. Prahalad S, Bove KE, Dickens D, et al. Etanercept in the treatment of macrophage activation syndrome. *J Rheumatol* 2001;28:2120-2124.
44. Abella EM, Artrip J, Schultz K, et al. Treatment of familial erythrophagocytic lymphohistiocytosis with cyclosporine A. *J Pediatr* 1997;130:467-470.
45. Mouy R, Stephan J-L, Pillet P, et al. Efficacy of cyclosporine A in the treatment of macrophage activation syndrome in juvenile arthritis: report of five cases. *J Pediatr* 1996;129:750-754.
46. Tsuda H. The use of cyclosporin-A in the treatment of virus-associated hemophagocytic syndrome in adults. *Leuk Lymphoma* 1997;28:73-82.
47. Uno M, Tsuchiyama J, Moriwaki A, et al. In vitro induction of apoptosis for nasal angiocentric natural killer cell lymphoma-derived cell line, NK-YS, by etoposide and cyclosporine A. *Br J Haematol* 2001;113: 1009-1014.
48. Battiwalla M, Melenhorst J, Sauntharajah Y, et al. HLA-DR4 predicts haematological response to cyclosporine in T-large granular lymphocyte lymphoproliferative disorders. *Br J Haematol* 2003;123:449-453.
49. Imashuku S, Teramura T, Morimoto A, Hibi S. Recent developments in the management of haemophagocytic lymphohistiocytosis. *Expert Opin Pharmacother* 2001;2:1437-1448.
50. Henter J-I, Arico M, Egeler RM, et al. HLH-94 a treatment protocol for hemophagocytic lymphohistiocytosis. *Med Pediatr Oncol* 1997;28:342-347.
51. Imashuku S, Hibi S, Kuriyama K, et al. Management of severe

- neutropenia with cyclosporin during initial treatment of Epstein-Barr virus-related hemophagocytic lymphohistiocytosis. *Leuk Lymphoma* 2000;3339–3346.
52. Goede JS, Peghini PE, Fehr J. Oral low dose etoposide in the treatment of macrophage activation syndrome. *Blood* 2004; 103:Abstract #3817.
53. Imashuku S, Teramura T, Kuriyama K, et al. Risk of etoposide-related acute myeloid leukemia in the treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. *Int J Hematol* 2002;75: 174–177.
54. Obama K, Tara M, Niina K. L-asparaginase induced complete remission in Epstein-Barr virus positive, multidrug resistant, cutaneous T-cell lymphoma. *Int J Hematol* 1999;69:260-262.
55. Mounier N, Simon D, Haioun C, et al. Impact of high-dose chemotherapy on peripheral T-cell lymphomas. *J Clin Oncol* 2002;20:1426-1427.
56. Reimer P, Ruedinger T, Schertlin T, et al. Autologous stem cell transplantation as first line therapy in peripheral T-cell lymphomas. A prospective multicenter study. *ASH Annual Meeting Abstracts* 2005;106:2074.
57. Mounier N, Gisselbrecht C, Biere J, et al. All aggressive lymphoma subtypes do not share similar outcome after front-line autotransplantation: A matched-control analysis by the Groupe d'etude des Lymphomes de l'Adulte (GELA). *Ann Oncol* 2004;15:1790-1797.
58. Tsuchiyama J, Imalo K, Yoshino T, et al. High-dose chemotherapy and autologous peripheral blood stem cell transplantation for treatment of unspecified peripheral T-cell lymphoma presented with hepatosplenomegaly and hypercytokinemia syndrome: report of three cases. *Ann Hematol* 2002;81:588-592.
59. Peniket A, Ruiz de Elvira M, Taghipour G, et al. An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. *Bone Marrow Transplant* 2003;31:667–678.
60. Henter JI, Samuelsson-Horne A, Arico M, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunotherapy and bone marrow transplantation. *Blood* 2002; 100:2367–2373.
61. Jordan M, Filipovich A. Hematopoietic cell transplantation for hemophagocytic lymphohistiocytosis: a journey of a thousand miles begins with a single (big) step. *Bone Marrow Transplant* 2008;42:433–437.
62. Imashuku S, Hibi S, Todo S, et al. Allogeneic hematopoietic stem cell transplantation for patients with hemophagocytic syndrome (HPS) in Japan. *Bone Marrow Transplant* 1999;23:569-572.
63. Doocey R, Toze C, Connors J, et al. Allogeneic hematopoietic stem cell transplantation for relapsed and refractory aggressive histology non-Hodgkin lymphoma. *Br J Haematol* 2005;131:223-230.
64. Horne A, Janka G, Maarten Egeler R, et al. Haematopoietic stem cell transplantation in haemophagocytic lymphohistiocytosis. *Br J Haematol* 2005;129: 622–630.
65. Baker KS, Filipovich AH, Gross TG, et al. Unrelated donor hematopoietic stem cell transplantation for hemophagocytic lymphohistiocytosis. *Bone Marrow Transplant* 2008;42:175–180.
66. Ouachee-Chardin M, Elie C, de Saint Basile G, et al. Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis: a single-center report of 48 patients. *Pediatrics* 2006;117:e743–e750.
67. Marsh R, Vaughn G, Kim M, et al. Reduced-intensity conditioning significantly improves survival of patients with hemophagocytic lymphohistiocytosis undergoing allogeneic hematopoietic cell transplantation. *Blood* 2010;116:5824-5831.
68. Cooper N, Rao K, Gilmour K, et al. Stem cell transplantation with reduced-intensity conditioning for hemophagocytic lymphohistiocytosis. *Blood* 2006;107:1233–1236.