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How can an internal medicine specialist save a patient with hemophagocytic lymphohistiocytosis (HLH)?

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Short title: HLH for internal medicine specialists

Abstract [max 250 words]

HLH (hemophagocytic lymphohistiocytosis; hemophagocytic syndrome) occurs when inflammatory reaction cannot stop on its own, but continues to self-accelerate with positive feedback loops. If not interrupted, this pathomechanism leads to death. HLH in adults is usually diagnosed based on HLH-2004 criteria, but its confirmation should not stop the diagnostic process. Finding the triggering factor (especially malignancy) is of utmost importance. Treatment strongly depends on the established trigger; based on etoposide HLH-94 protocol (adjusted for adults) is used in many instances. Diagnostic process should not unnecessarily delay the treatment, patients in severe or quickly deteriorating clinical condition require its fast initiation. Provided progressive character of HLH, time is extremely important. Prompt diagnosis and treatment, frequently made by an internal medicine specialist, is life-saving.

Aim of this review is to raise HLH awareness among internal medicine specialists and to provide advice on HLH management tailored for this group of physicians. Suggested approach is based on the latest recommendations by the Histiocyte Society and include novel insights based on the Authors’ experience.
Keywords
HLH, hemophagocytic lymphohistiocytosis, hemophagocytic syndrome, hyperferritinemia, adults

Main body

Why is HLH important for internal medicine specialists?

HLH (hemophagocytic lymphohistiocytosis; hemophagocytic syndrome) is a syndrome of uncontrolled hyperinflammation, which leads to death when left untreated\(^1\). Its symptoms essentially resemble infection, without obvious characteristic differences, and patients are usually treated for sepsis – but have no chance to be cured with antibacterial therapy. In effect, HLH remains severely underdiagnosed and many patients die without any attempt of effective treatment (which is widely available). Role of internal medicine specialists in saving HLH patients is crucial as frequently they are first specialists who can suspect HLH, diagnose it and, if possible, start treatment.

HLH is a rare syndrome – data for adults from Sweden show 3.6 cases per million inhabitants annually\(^2\), but this data includes only HLH associated with malignancy, what suggests it may be at least two times more frequent. It is also heavily underdiagnosed. In Poland at least 250 new cases of HLH in adults may be expected every year, but unfortunately majority of those patients are not diagnosed and eventually die untreated.

Aim of this review is to raise HLH awareness among internal medicine specialists and to provide advice on HLH management tailored for this group of physicians. Suggested approach is based on the latest recommendations by the Histiocyte Society and include novel insights based on the Authors’ experience\(^3\).
**What is HLH?**

HLH occurs when inflammatory reaction cannot stop on its own, but continues to self-accelerate with positive feedback loops. Its mechanism is well described in primary HLH where genetic defect in cytotoxic granule pathway causes lack of cytotoxic activity of T-lymphocytes and NK-cells. Although unable to kill target cells, they retain ability to release cytokines stimulating macrophages, which in turn stimulate cytotoxic cells causing a vicious circle of positive feedback loops. Genes involved in this process are shown in Figure 1. Severe biallelic mutation in this pathway will cause HLH onset in early childhood, but less severe defects were also found in adults\(^4\,5\).

This mechanism is characteristic for familial (primary) HLH. Recently also defects in inflammasome function were found to be associated with HLH, but a vast majority of adult patients do not have any identifiable genetic abnormality (but probably have some other, not yet known predisposition as HLH is very rare). In such situation HLH is described as secondary.

Pathologic inflammation has to be induced by a triggering factor. In case of lack of any cytotoxic activity, every infection can start HLH in an infant. Adults have a higher threshold for HLH induction. The most important triggering factors are: infections, malignancies and autoinflammatory disorders. Among infections, they are usually viral, with leading role of EBV. CMV, parvovirus or influenza A H5N1 were also described\(^6\), as well as bacterial, fungal or parasitic triggers\(^7\). Malignancies inducing HLH are usually lymphomas, especially T-cell, but also myeloid malignancies and solid tumors are frequently reported\(^8\). HLH may also occur in patients with immune suppression after chemotherapy, receiving immunosuppressive drugs or in HIV infection – in such cases it is usually caused by a secondary infection. Autoimmune disorders include Stills’ disease, lupus, systemic juvenile idiopathic arthritis and others – such cases of HLH are frequently described as MAS (macrophage activation syndrome).

Term MAS can be also used in less severe than HLH cases of severe autoinflammation. HLH is always at the far end of the inflammatory continuum. Different, often misleading, names used for description of similar symptoms are summarized in **Table 1**.
When should I suspect HLH?

In a patient with intense, progressive inflammation with recurrent fever, cytopenia and splenomegaly or coagulopathy. These manifestations can be accompanied by organomegaly, lymphadenopathy, rash, arthralgia, icterus, purpura, edema, dyspnea and progress to multiorgan failure (MODS). These symptoms may be produced by both a triggering factor and HLH itself, but their presence should raise suspicion of HLH. Laboratory results frequently include hypertriglyceridemia, hyperbilirubinemia, transaminitis, elevated lactate dehydrogenase and D-dimer levels.

Patient, despite looking “septic”, does not respond to empiric antimicrobial therapy. Important trait is symptom progression, which can become rapid – HLH is also diagnosed at ICU. HLH, as an intense inflammation is unlikely in an afebrile patient.

Is there any single pathognomonic symptom of HLH?

No single clinical or laboratory feature is pathognomonic for HLH. Extreme hyperferritinemia is the only commonly present abnormality which may be to some extent characteristic. HLH patients may present with values exceeding 10,000 ng/ml (sometimes even 100,000 ng/ml). Only a subset of patients are characterized by such a high values and hyperferritinemia may have multiple other causes in adults e.g. hemochromatosis, transfusions or liver failure. Although its predictive value is not satisfactory, disproportionately high hyperferritinemia in a febrile patient should always raise suspicion of HLH.

Hemophagocytosis is phagocytosis of blood cells by activated macrophages observed in microscopical evaluation of biological material, most commonly bone marrow smear. It is a base for the name “hemophagocytic syndrome”, but confirmation of its presence is neither required nor sufficient for the diagnosis of HLH. Hemophagocytosis can be present in many inflammatory conditions: sepsis, influenza, leishmaniasis, malaria, active rheumatoid disorders, and after blood transfusions. Overdiagnosing “hemophagocytic syndrome” based on presence of hemophagocytosis and selected
other symptoms, but not fulfilling the remaining diagnostic criteria may have detrimental consequences, leading to unsuccessful treatment of HLH without making the right diagnosis.

On the other hand, hemophagocytosis is considered one of the late HLH symptoms (it was found in 32% of children at admission and 85% at HLH diagnosis\textsuperscript{13}) and neglecting diagnosis of “hemophagocytic syndrome without hemophagocytosis” (which is not yet visible) is life-threatening.

Increased concentration of soluble interleukin 2 receptor (sIL-2R), also known as sCD25, although in clinical practice used mostly for diagnosing HLH, is also elevated in multiple other conditions like autoimmune diseases, neoplasms (notably lymphoproliferations), and infections\textsuperscript{14}. Although by no means pathognomonic, its elevated concentration can help guiding differential diagnosis towards HLH and low values are helpful in ruling HLH out\textsuperscript{15}. High sCD25/ferritin ratio suggests lymphoma as HLH trigger\textsuperscript{16}. Key problem of this useful test is its availability in only highly specialized centers.

Determination of Natural Killer cell activity (gradually replaced by analysis of perforin and CD107a\textsuperscript{17}) is important mostly as screening of genetic defects responsible for familial HLH. Undoubtedly its importance in adults is much lower than in children. Low NK cell activity, although key to the mechanism of familial HLH, is by no means pathognomonic for HLH – it was found also in 96% of patients in septic shock\textsuperscript{18}.

How to make the diagnosis?

Diagnosis of HLH is based on the confirmation of a constellation of hyperinflammation symptoms, while presence and intensity of each one of them varies between the patients. The most widely accepted is fulfillment of at least 5 out of 8 HLH-2004 criteria\textsuperscript{19} (Table 2). They were created by a group of experts as inclusion criteria for a pediatric clinical trial, what is frequently underlined as their limitation in adults. Despite that, they are most widely used standard also in this population. Two out of eight HLH-2004 criteria (NK-cell activity and sCD25 concentration) are very difficult to test in the general practice, as discussed above. In a rapidly deteriorating patient prompt initiation of therapy is life-saving. In such cases a simplified system was proposed by Wieslaw Wiktor-Jedrzejczak\textsuperscript{20}: patient
should convincingly fulfill at least 4 out of available 6 HLH-2004 criteria including ferritin higher than 2000 ng/ml and there is no other than HLH cause for observed abnormalities.

Independent system overcoming the main limitations of HLH-2004 is the HScore\textsuperscript{21}. It was designed using only widely available parameters (established by a worldwide expert Delphi survey\textsuperscript{22}) and based on data of adult French patients. Its design is more complex than HLH-2004 (parameters can have more than one threshold and each parameter has a different weight), moreover it gives a probability, not a certain diagnosis. HScore can be easily calculated online at: \url{http://saintantoine.aphp.fr/score/}.

MAS has different pediatric criteria (e.g. Ravelli criteria in sJIA\textsuperscript{23} or MH Score\textsuperscript{24}) which allow diagnosis at much earlier stage than HLH-2004, but in some MAS patients hyperinflammation also fulfills HLH-2004 criteria.

Diagnostic process has to be continued after the HLH diagnosis, which also does not indicate the necessity of starting the treatment. It only suggests that the inflammation is very intense and soon may become life-threatening. Aggressive diagnostic approach to establish the trigger is crucial for choice of optimal treatment. Wide panel of infectious agents should be tested, always including EBV and HIV and then dependent on patient history including travel exposure. Screening for autoimmune diseases should also be initiated. Adult patients are at high risk of underlying malignancy and all effort should be made to diagnose it. In addition to bone marrow testing bone marrow, other biopsies are usually required (guided by CT and ideally by PET CT imaging). Also repeated biopsies may be needed for occult, difficult to diagnose lymphoma (like intravascular B-cell lymphoma).

Patient fulfills the criteria. What should I do now?

Consult hematologist, if it has not been already done. Perform all suggested lab tests, imaging and biopsies (including trephine biopsy) as soon as possible. If you need to start treatment, store samples for genetic testing. If patient is deteriorating, diagnostic process should not delay the treatment! Full treatment at least in Poland is available only in hematology wards.
Prompt initiation of all these actions is crucial, but requires a very cautious approach. While current problem is underdiagnosis of HLH, overdiagnosis is also possible. This may occur when two or three conditions together produce abnormalities in parameters used as HLH criteria. For example patients with chronic liver failure frequently have splenomegaly (portal hypertension), hyperferritinemia (released from damaged liver), some degree of anemia and thrombocytopenia and may occasionally have infection with fever. Such patient would not benefit from HLH treatment.

Additionally, there are numerous “HLH mimics”\textsuperscript{25} which despite fulfilling HLH criteria require different treatment. They include infections like visceral leishmaniasis, tuberculosis, mycobacteriosis, histoplasmosis, infection with Ehrlichia, Bartonella and Brucella species, disseminated adenovirus, and disseminated herpes simplex virus. In the course of above mentioned infections, HLH-2004 criteria may be fulfilled, but they require antimicrobial treatment instead of immunosuppression like in HLH treatment.

\textbf{Initial treatment}

Steroids should be initiated if patient is at risk of fast deterioration, and a prompt intervention of internal medicine specialist can be life-saving. Depending on the clinical context, the treatment may include methylprednisolone pulses or dexamethasone 10 mg/m\textsuperscript{2} – as an initiation of the HLH-94 protocol\textsuperscript{3}. Another important treatment method, which may be delivered by internal medicine specialist are intravenous immunoglobulins (IVIG, up to 1.6 g/kg split over 2-3 days)\textsuperscript{8,26}. This treatment may stop moderate HLH or slow down the progression of more severe HLH giving time for diagnostic procedures and further treatment in hematology ward.

\textbf{Hematological treatment}

Effective treatment of severe HLH is based on cytostatic agent etoposide (VP-16). The first widely used treatment protocol was HLH-94\textsuperscript{27} (\textbf{Table 3}) consisting of etoposide, dexamethasone and (after 8 weeks) cyclosporin A (CsA). In a similar HLH-2004 treatment protocol main difference was the use of cyclosporin from the beginning of therapy\textsuperscript{19}. HLH-2004 did not show significant survival advantage.
over HLH-94\textsuperscript{28}, so the latter remains standard for HLH treatment in children. Cyclosporin A requires concentration measurements and toxicity assessment and can be replaced with tacrolimus\textsuperscript{29}.

Apparently, pediatric protocols are overly toxic for adults. Adjustment of HLH-94 is based on regimen proposed by prof. Jan-Inge Henter for treatment of HLH triggered by avian influenza\textsuperscript{6}. Dose of etoposide is reduced from 150 mg/m\textsuperscript{2} to 50-100 mg/m\textsuperscript{2}, additionally also in the first two weeks it is administered once (not twice) a week (\textbf{Table 3}). Detailed recommendations of the Histiocyte Society on the use of etoposide in HLH (including dose reductions) were published in 2018\textsuperscript{30}.

As etoposide is mutagenic and its use is associated with risk of secondary leukemia. At present experience with this complication in adult HLH is limited, but this risk is lower than morbidity and mortality of severe HLH\textsuperscript{30}. Only two children in two large pediatric studies developed leukemia: 1 in 368 subjects in HLH-2004\textsuperscript{28} and 1 in 249 individuals in HLH-94 study\textsuperscript{31}. These events were observed at a median follow-up of 5.2 and 6.2 years after etoposide exposure, respectively. In 81 Japanese patients with EBV-triggered HLH one case of leukemia was described\textsuperscript{32}. In adult patients without malignancy, the cumulative dose of etoposide below 2-3 g/m\textsuperscript{2} is recommended\textsuperscript{32}. Adult patients frequently do not need the full 8 week-course of therapy and later maintenance, so the cumulative dose of etoposide is much lower than in children.

**Does the HLH diagnosis always require etoposide treatment?**

Fulfillment of 5 or even 8 HLH-2004 criteria does not mean, that patient has to receive HLH-94 protocol\textsuperscript{30}. Treatment should be tailored for each patient and depends on the underlying trigger. If HLH is diagnosed early enough, it may be stopped with steroids alone (with or without IVIG). Other important variations in approach include the following situations.

Rituximab can be an important addition in HLH associated with EBV infection\textsuperscript{33}. EBV viremia should be confirmed with PCR, levels above $>10^3$ copies/mL were found in over 90% of patients at first presentation\textsuperscript{34}.  


Malignancy-associated HLH initially may require HLH-specific approach to stop the cytokine storm, but eventually therapy should be targeted against the triggering neoplasm. In lymphoma treatment regimens containing etoposide can be chosen (e.g. CHOEP, DA-EPOCH).\textsuperscript{36}

HLH after chemotherapy or after stem cell transplantation is difficult to diagnose. Additional cytotoxic activity of etoposide can prolong cytopenia and impair the potential to fight the underlying infection, which is the usual trigger in such cases. Antimicrobial treatment, steroids and IVIG are preferred. Also suspected relapse of HLH may be associated with infection. Wide antimicrobial prophylaxis is recommended.

Cytokine release syndrome – complication after use of CAR (chimeric antigen receptor) T-cells or blinatumomab is a specific form of iatrogenic HLH. It has its’ own specific diagnostic criteria and treatment is based on steroids and tocilizumab (antibody against IL-6 receptor).\textsuperscript{35,36}

**MAS**

Macrophage activation syndrome is HLH in patients with autoimmune/autoinflammatory disease. It can also be triggered by infection, not the disease itself.\textsuperscript{37} First line treatment is steroids (e.g. pulses of methylprednisolone 1 g/day for 3-5 days).\textsuperscript{38} Treatment specific for MAS may include anakinra (anti-IL-1 therapy),\textsuperscript{39} tocilizumab\textsuperscript{40} or CsA. Some patients with very severe or refractory MAS-HLH may require etoposide therapy.\textsuperscript{30}

**End-of-life HLH**

Many patients who are in the last days of their life due to various, but usually advanced diseases (e.g. lymphoma or other malignancy progressing after several lines of treatment) can present with many of the HLH-2004 criteria, sometimes can even fulfill most of them. Obviously it is not emergence of HLH as additional disease, but progressing multiorgan failure causing multiple abnormalities – also those defined by the HLH-2004 criteria. Such patient will certainly not benefit from this “new diagnosis” and etoposide treatment, which can only shorten his life. Steroids are used in palliative care alleviating some of such inflammatory symptoms without need of diagnosing HLH.
Also patients with newly diagnosed (or even not yet diagnosed) malignancy, who seek professional help too late (e.g. when they neglected alarming symptoms for a long time) can be in similar situation. They can fulfill some of the HLH-2004 criteria but frequently they are rather equivalent of their severe clinical condition rather than beginning of HLH. Some of such patients have already crossed “point of no return” – their imminent death cannot be reversed with currently available methods. This tragic situation can also occur in patients with “real HLH” when cytokine storm is already so intense that it cannot be stopped with any presently available treatment.

**Salvage therapy**

HLH reactivation may be caused by too moderate or too quickly tapered treatment – in such case intensification of standard therapy may succeed. Caution is advised because there is always a risk of secondary infection falsely diagnosed as HLH relapse. The only HLH salvage therapy tested in adults in a prospective trial is DEP regimen (liposomal doxorubicin, etoposide and methylprednisolone)\(^4^1\).

Plasmapheresis and cytokine adsorption columns can be of great help in fighting refractory HLH\(^4^2,4^3\). Ruxolitinib (JAK kinase inhibitor) has a high potential in HLH and may be used in a refractory setting\(^4^4,4^5\). As interferon gamma (IFN\(\gamma\)) was found to be the key agent in HLH cytokine storm\(^4^6\), an anti-IFN\(\gamma\) antibody was introduced. Emapalumab was approved by the FDA (Food and Drug Administration) in November 2018 as a second line treatment of primary HLH in children and adults\(^4^7\).

Alemtuzumab (anti-CD52 antibody) was found effective both in first line therapy in children with familial HLH\(^4^8\) and as a salvage therapy in children\(^4^9\) and in adults\(^5^0\), as a bridge to allogeneic hematopoietic stem cell transplantation (allo-HSCT). Allo-HSCT itself is indicated in adults with primary or relapsed/refractory disease\(^3,2^6,2^9\). Diagnosis of primary HLH and indications for allo-HSCT based on genetic results should be carefully analyzed in adults to exclude genetic alterations without or with little clinical significance – like perforin A91V polymorphism present in 10% of population\(^5^1\).
What if patient with history of HLH presents with a fever?

This can be a problem at internal medicine ward when a febrile patient with previous history of HLH is admitted. First step is to repeat all HLH-relevant tests to check if it is relapse of HLH. Past history is important, but in case of (presumed) HLH relapse it is crucial to always re-determine the trigger. Patient with an excellent response to HLH treatment may relapse with a different (e.g. malignant) trigger. In our observation, young man with previously treated in a different center for EBV-triggered HLH, at relapse was diagnosed with T-cell lymphoma, even though EBV viremia was present again.

Should I diagnose and treat relatives?

This relevant question is not fully answered in adult population. In children, which usually have a strong genetic predisposition, it is crucial to investigate siblings for the same mutation as proband. It was shown that preemptive allo-HSCT in unaffected children has better outcomes than if treatment was started at the first HLH symptoms\(^5^2\). If the proband developed HLH after 18 years of age the genetic predisposition in his siblings usually does not require up-front allo-HSCT.

An HLH patient’s relative undergoing a severe febrile episode should have basic HLH parameters assessed (complete blood count with differential, ferritin, triglycerides, transaminases and presence of hepatosplenomegaly). Good practice is to perform basic HLH tests in patient’s siblings in order to have baseline results for comparison in case of a severe febrile episode. Adult siblings may have e.g. anemia, hyperferritinemia due to hemochromatosis or hypertriglyceridemia due to dyslipidemia. All of these abnormalities if found during a febrile episode may cause unnecessary fear of HLH onset, therefore they should be reassessed at least every 2-3 years. Unaffected sibling negative for genetic mutation may also benefit from such screening because predisposition in his family may be associated with mutation in a different gene (not yet attributed to HLH).

Conclusions

HLH is a rare but life threatening syndrome, which when promptly diagnosed and managed may be resolved. It is a disease of vicious circle of hyperinflammation which if not stopped leads to multiple
organ failure. In adults it can be triggered by many different primary disorders such as neoplasia, viral and less frequently bacterial and fungal infections as well as autoimmune diseases. Additionally, especially in younger adults it may still be due to inherited mutations of genes affecting activation of cytotoxic cells. Diagnosis is based on confirmation of co-occurrence of several symptoms with hyperferritinemia being the most characteristic. In majority of patients only etoposide-based therapy is able to stop its progress and only when it is instituted prior this syndrome will pass into irreversible stage. Hence, awareness of internal medicine specialists about is existence and methods of identification is critical.

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Figure 1. Genetic background of primary HLH – cytotoxic granule pathway. Name of the syndromes (blue boxes) are next to names of proteins which defect causes each syndrome (in white).

Abbreviations: ER, endoplasmic reticulum; FHL, Familial Hemophagocytic Lymphohistiocytosis, HPS, Heřmanský-Pudlák Syndrome; CHS, Chédiak Higashi Syndrome; GS II, Griscelli syndrome type II
Table 1. Similar symptoms – different names

| Term                  | Description                                                                                                                                                                                                 |
|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| HLH                   | Hemophagocytic lymphohistiocytosis – usually defined as fulfilling the HLH-2004 criteria                                                                                                                      |
| Hemophagocytic syndrome| Slightly wider term than HLH – incorporates also patients diagnosed e.g. with HScore                                                                                                                      |
| MAS                   | Macrophage Activation Syndrome – hyperinflammation syndrome caused by autoimmune/autoinflammatory disease. Term MAS-HLH is also in use. It can be much milder than HLH (e.g. when diagnosed with Ravelli criteria) or, much less frequently fulfill HLH-2004 criteria. Historically, it used to be a synonym for HLH/hemophagocytic syndrome |
| MAS-sepsis, Hyperferritinemic sepsis | These and other similar terms describe hyperinflammatory variant of sepsis, which is much more common than HLH and should not be mistaken with HLH or MAS as defined above.                                            |
| CRS                   | Cytokine Release Syndrome – occurs after use of certain novel immunotherapies (blinatumomab, CAR-T cells).                                                                                                     |
| Cytokine storm syndrome| Probably the widest and least defined term – may include all of the above.                                                                                                                                 |

All of the abovementioned terms are used by different authors with different meanings, sometimes interchangeably. Caution and checking for exact definition in every paper is advised.

Table 2. HLH-2004 diagnostic criteria

A Molecular diagnosis consistent with HLH

B 5 out of 8 criteria:

1. Fever
2. Splenomegaly
3. Cytopenia of ≥2 out of 3 lineages:
   - Neutrophils <1.0 × 10⁹/L
   - Hb < 9.0 g/dL
   - PLT < 100 × 10⁹/L
4. Hypofibrinogenemia and/or hypertriglyceridemia:
   - Fibrinogen ≤1.5 g/L (150 mg/dL)
   - Triglycerides ≥3.0 mmol/L (265 mg/dL)
5. Hemophagocytosis
6. Ferritin ≥ 500 ng/mL
7. Low NK-cell activity
8. sCD25 (sIL-2R) ≥ 2,400 U/mL
Abbreviations: Hb, hemoglobin; PLT, platelet count; NK, Natural Killer; sCD25, soluble CD25 (Cluster of Differentiation 25); sIL-2R, soluble interleukin 2 receptor

Table 3. Comparison of HLH treatment regimens

| Week | 1 – 2                      | 3 – 4                      | 5 – 6                      | 7 – 8                      |
|------|---------------------------|---------------------------|---------------------------|---------------------------|
| HLH-94 |                         |                           |                           |                           |
| VP-16 | 2×150 mg/m²/wk           | 1×150 mg/m²/wk            |                           |                           |
| Dex   | 10 mg/m²/d                | 5 mg/m²/d                 | 2.5 mg/m²/d               | 1.25 mg/m²/d             |
| CsA   |                           |                           |                           | After 8 weeks             |
| HLH-2004 |                       |                           |                           |                           |
| VP-16 | 2×150 mg/m²/wk           | 1×150 mg/m²/wk            |                           |                           |
| Dex   |                           |                           |                           |                           |
| CsA   |                           |                           | Concentration 200 µg/L    |                           |
| HLH-94 adjusted for adults |           |                           |                           |                           |
| VP-16 | 1×50-100 mg/m²/wk        |                           |                           |                           |
| Dex   |                           |                           |                           |                           |
| CsA   |                           |                           |                           | Possible after 8 weeks    |

Abbreviations: VP-16, etoposide; Dex, dexamethasone; CsA, cyclosporin A; wk, week; d, day