Treatment of hemophagocytic lymphohistiocytosis

Yini Wang and Zhao Wang

Purpose of review
Hemophagocytic lymphohistiocytosis (HLH) is a condition of uncontrolled immune activation with a high mortality rate. The recommended therapeutic guideline for HLH was published by the Histiocyte Society in 1994 and revised in 2004, which greatly improved the survival in patients with HLH. However, HLH is still a refractory disease for which the search for novel treatments continues. This article overviewed recent advances in treatment of HLH.

Recent findings
Current practices in treatment extend from chemo-immunotherapy to some new cytokine-targeting biologicals, which are more effective to eliminate pathologically activated T cells and resist exaggerated cytokine storm. Preliminary results showed that some novel approaches to refractory HLH would potentially improve outcome of the fatal disease. Allogeneic hematopoietic stem cell transplantation after HLH remission represents the final solution for replacing defective cytotoxic T cells and even treating some underlying disease processes to prevent disease recurrence.

Summary
A uniform protocol and algorithm for the treatment would not be appropriate for each patient given the heterogeneity of the underlying conditions. Further improvements in therapy require prospective trials to develop reasonable strategies for HLH patients in different subtypes, based on the underlying trigger, disease severity, as well as genetic background.

Keywords
biologicals, hematopoietic stem cell transplantation, hemophagocytic lymphohistiocytosis, salvage therapy

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition clinically characterized by overactivation of the immune system leading to severe hyperinflammation and immunopathological manifestations [1]. It is comprised of a wide spectrum of nonspecific inflammatory symptoms, but diverse etiological categories. Based on the underlying etiologies, HLH is generally divided into a primary form of inherited gene defects and a secondary form complicates various medical conditions, mainly including infection, malignancy, and autoimmune disease. The therapeutic guideline for HLH published by the Histiocyte Society in 1994 was a milestone in HLH treatment that improved the 5-year survival rate of HLH patients from less than 10% to about 50% [2]. However, HLH is still a refractory disease and most experiences of diagnosis and treatment were derived from children with inherited gene defects. In the past decades, it has been clearly recognized that HLH can affect all ages and the primary form is only a tip of the iceberg of HLH. More issues about treatment are worthy of discussion, such as the value of conventional therapy in different subtypes, the novel approaches of treatment, and the individualized therapy strategies. Current opinions of how to treat HLH are renewed constantly with the recognition of the essence of HLH.

CONVENTIONAL INDUCTION THERAPY OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

HLH was usually fatal with an average survival of 2 months before the first therapeutic guideline (HLH-94 protocol) was set up. This protocol, including dexamethasone and etoposide for 8-week-induction therapy, increased the disease response rate from less than 10% in the past few years to about 70%. Subsequent allogeneic hematopoietic stem cell

Department of Hematology, Beijing Friendship Hospital, Capital Medical University, Beijing, China

Correspondence to Dr Zhao Wang, Professor, Department of Hematology, Beijing Friendship Hospital, Capital Medical University, No. 95, Yong'an Road, Beijing 100050, China. Tel: +86 10 63138303; e-mail: zhaowww263@outlook.com

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KEY POINTS

- HLH-94 is still a reliable protocol of induction treatment for both children and adults.
- Novel approaches to refractory HLH may achieve dramatic improvements in survival in future.
- Allo-HSCT is a current ultimate solution for primary HLH, and also has potential application to adults.

transplantation (HSCT) benefited about 50% of patients to get a long-term survival [3]. HLH-2004 was a revised pattern of HLH-94, which aimed to enhance induction treatment by starting cyclosporine A (CsA) simultaneously with etoposide to limit the proliferation and activation of immune cells and to halt the cytokine storm [4]. So far the treatment results have not been published, preliminary analysis was only presented at the last Histiocyte Society annual meeting. It was seemed that the response rate was a little bit better than HLH-94, but did not reach statistical significance. Because there is no evidence to strongly support that patients would get more benefit from HLH-2004, we do not recommend using CSA at the start of induction treatment if the underlying etiologies are not clear or malignancies cannot be ruled out. The patients recruited for HLH-94 trial were mainly children of primary HLH, lacking adult patients and many other subtypes of secondary HLH. The remaining interesting issues are whether the conventional therapy applies to secondary HLH and whether the algorithm is adaptive to adult patients.

Epstein–Barr virus-associated HLH (EBV-HLH) is most common in both children and adults. A study [5] from Japan reported that up to 90% of EBV-HLH patients achieved remission after immunochemotherapy based on the HLH-94/HLH-2004 protocol. Other reports had backed up this notion that induction therapy with etoposide within 4 weeks was associated with better outcomes in EBV-HLH cohort [6,7]. Similar to the primary HLH, etoposide is believed to play a critical role in treatment of EBV-HLH. That is because etoposide not only induces apoptosis and limits the release of inflammatory cytokines, but also inhibits EBV nuclear antigen synthesis and transformation of EBV-infected cells [8,9]. However, EBV-HLH is a heterogeneous disorder, ranging from self-limiting to aggressive or even fatal. The therapeutic effects are influenced by many factors, such as the severity of disease course, EBV load, and T-cell clonality. There was a report that T-cell clonality was useful to predict the therapeutic response of patients with EBV-HLH [10]. Therefore, the conventional therapy is basically applicable to EBV-HLH, but a novel approach specific to refractory EBV infection is necessary. Macrophage activation syndrome (MAS) is another form of secondary HLH, induced by autoimmune diseases. A multinational, multicenter study [11] of MAS complicating systemic juvenile idiopathic arthritis (sJIA) showed all patients were given corticosteroids, and 61% received CsA, but only 12% of the patients were administrated with etoposide. The standard HLH-94 algorithm is not recommended to use for patients with MAS, wherein pulse methylprednisolone is the preferred way of care [12]. The main concerns about no etoposide-based induction therapy are the relatively high response rate to single glucocorticoids treatment and potential toxicity of etoposide. However, HLH-2004 should be a considerable way of induction therapy for patients in whom age is older or MAS remains active after using of corticosteroids and CsA [13▪]. There are few series data from malignancy-associated HLH due to the rare incidence in children. CHOP was used widely for lymphoma-associated hemophagocytic syndromes (LAHS) in adult patients but did not achieve good remission [14,15]. Most of the reports showed that underlying lymphoma was associated with a poorer prognosis in comparison with other subtypes.

Since research on adult HLH only began several years ago, there is no specific therapeutic guideline for adult patients. The initial treatment was variable in each clinical center. There is a lack of sufficient data to answer the question of whether HLH-94 is adaptive to adult patients. A recent published retrospective multicenter study [16▪▪] indicated that the use of etoposide as a first-line treatment tended to be associated with a better outcome. This is the published largest population-based analysis of adult HLH patients. It indicated that adult patients treated with etoposide-based initial therapy had a tendency to get a better outcome than no etoposide-based therapy. In contrast, another study [14] found that there was no significant difference in the overall survival between the cohorts receiving etoposide or nonetoposide-based regimens. Our experience was based on 576 cases of adult HLH patients, of whom 277 cases were treated with HLH-94 or HLH-2004. The response rates were 61.4 and 51.9% in cohort of etoposide or nonetoposide-based therapy, respectively. Most of the patients who achieved remission from nonetoposide-based regimen were MAS. The response rate of primary HLH in adults was similar to it in children, but the LAHS group was much lower than other etiological categories. Additionally, the algorithm in adults usually needs to be modified because of the relatively poor tolerance to etoposide

in adults, most notably in bone marrow suppression. Henter *et al.* [17] emphasized the importance of age-adapted dosing (100 mg/m^2 down to 50 mg/m^2 in elderly patients). Our experience also supported that reduced-dose etoposide should be more adaptive to adult patients.

In general, conventional induction therapy (HLH-94/2004) should be a practical means of inducing remission in active HLH patients at present, both in children and adults, unless a new effective treatment is proved. But the response rate during the active phase is lower in adults than in pediatric patients. This disparity might be due to the more complex etiology and varied inducing factors of adult HLH. HLH-94-like treatment, modified algorithm, frequently is applied in patient's individual situation.

NEW APPROACHES TO SALVAGE THERAPY

Although the improvements are made to the HLH-94 protocol, an estimated 30% of HLH patients do not respond to conventional therapy. The search for novel treatments continues to reduce HLH mortality. One single-center clinical study [18] with 38 patients showed that initial treatment combined with antithymocyte globulins (ATGs) increased the complete response rate to 73%; however, the early recurrence rate was also high, and there was no superiority in long-term prognosis. Another pediatric study of hybrid immunotherapy, the so-called HIT-HLH trial, is in progress. DEP regimen, a salvage treatment comprising of liposomal doxorubicin, etoposide, and methylprednisolone, is the first prospective clinical trial for adult HLH [19▪▪]. It showed an encouraging overall response (76.2%) and tolerance in adult refractory HLH patients. Because the secondary form is the majority of adult HLH, this regimen might bridge the transition from induction therapy to etiology therapy. Some other approaches have been tried in small cohorts. Splenectomy was reported to be an effective means to treat refractory HLH with unknown cause [20▪]. In that cohort, the evidence of lymphoma was found in spleen in seven of the 19 patients. It was considered to be valuable in treatment as well as in diagnosis for refractory or relapsed HLH with unclear etiology.

With the development of pathogenesis of HLH, the treatment strategies are beginning to shift from overall immunosuppression towards biologicals, which are more targeted approaches. Alemtuzumab, a monoclonal antibody to CD52, has a rapid and efficient depletion of CD52-expressing cells. Based on its critical role of T cells in HLH pathogenesis, it resulted in significant response against refractory HLH [21]. It might be adaptive to patients with genetic defects or immunodeficiencies. But it is unclear whether the significant immune clearance is suitable because the underlying causes of HLH in adults are varied. Because interferon gamma (IFN-γ) has been shown to play a critical role in HLH in animal models, it has a potential to be a promising approach for refractory HLH. Recent report on a phase II clinical trial indicated that refractory primary HLH, as well as secondary, could achieve good response to IFN-γ neutralization agent [22▪▪]. The treatment was well tolerated as well. Some cytokine-targeting biologicals are tried to use in HLH, especially in MAS, because of the overwhelming inflammation caused by a 'cytokine storm'. Inhibitors of tumor necrosis factor (TNF-α), interleukin-6 (IL-6), or IL-1β were found to be effective in several case reports [23,24,25▪]. But the actual benefit from biologicals is still controversial because they have also been associated with the HLH development in some autoimmune disorders and in hematological neoplasms [26▪▪,27▪▪]. On our view, individual cytokine-targeting biological might only partially work on the pathogenesis and play a role in specific disease. It should not be a recommended first-line choice before the underlying etiologies are clear because the cytokine profile of HLH patients can vary with underlying diseases. A recent study [28▪▪] showed that ruxolitinib might be a novel approach for primary HLH therapy, which successfully treated two cytotoxicity impaired murine models. The JAK1/2 signaling pathway is downstream of several key inflammatory cytokine receptors. The inhibitor ruxolitinib has ability to block multiple cytokine-mediated signals, which involved in the course of HLH. Further study should be carried out to prove the therapeutic effect in human. Other novel targets, such as high mobility group box 1 (HMGB1) and IL-33 have already been demonstrated in other models of HLH [29▪,30▪]. These studies indicated that agent working on cytokine signaling pathways could be more effective to control 'cytokine storm'.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Allogeneic HSCT (allo-HSCT) is currently the only permanent solution for primary HLH because of the hereditary immunodeficiency. Because recent study proved that primary HLH could last onset at adulthood, immunologic assays and gene sequencing are important for both children and adults. It helps us determine whether the patients inevitably require HSCT for prolonged survival. But it is still a dilemma that a healthy mutation gene carrier has an urgent need for HSCT and the appropriate time. Because myeloablative conditioning (MAC) regimens were

reported of high transplant-related mortality and morbidity, recent research studies focus on the benefit from a reduced-intensity conditioning (RIC) regimen. Although the RIC regimen has substantially decreased toxicity, the high incidence of mixed chimerism is encountered. The risk of mixed chimerism depends on underlying disease, stem cell source, and alemtuzumab regimen. Patients who received a cord blood graft or a proximal or higher dose of alemtuzumab schedule experienced higher rates of mixed chimerism [31▪]. A study [32] in murine familial hemophagocytic lymphohistiocytosis indicate that mixed hematopoietic or cytotoxic T lymphocyte chimerism, with an engraftment of only 10–20% of perforin-expressing cells, is sufficient to prevent HLH development. A recent study [33▪▪] on patients also showed that a donor chimerism of about 20–30% is protective against late reactivation. All these study results supported that RIC regimen might be a reasonable approach on allo-HSCT for HLH patients.

However, lower mixed chimerism levels must not but potentially result in recurrences. HSCT in adult HLH patients was reported sporadically or in small cohorts. It has not been recommended for adult patients mainly because there has been no definite evidence that adult patients could get benefit from HSCT. A comparative study [34] reported that adult HLH patients undergoing HSCT were at increased risk of mortality compared to younger patients. Recently, a single-center study [35▪] reported an encouraging result of MAC-based allo-HSCT in a cohort of 30 adult patients. Twenty-six out of 30 patients in this cohort were secondary HLH, including lymphoma and EBV. We think that HSCT might be an effective treatment for adult HLH, whereas underlying disease control is essential for the treatment in the late stages. The grafts not only have ability to repair gene defects, but also can resist against aggressive tumor through graft-versus-tumor effect. Larger clinical trials are warranted to support this viewpoint.

Autologous HSCT (auto-HSCT) was considered to be applicable to some subtypes of HLH, such as lymphoma and sJIA. But there is lack of updated data. A new research trend in HLH treatment is to combine auto-HSCT with gene therapy to correct the genetic defect. Transfer of a functional perforin gene into autologous hematopoietic stem cells from perforin-deficient mice restored perforin expression, partially repaired the cytotoxic defect, and improved HLH symptoms [36]. Gene transfer of SAP also worked on a mouse model of XLP as well [37]. It will be a great progress in HLH therapy, if this approach can be successfully replicated in human. We suppose that specific gene repairing may be an effective means of treating primary HLH with lower systemic toxicity and transplantation-related mortality than allo-HSCT. Of note, transplanted patients have been ironically reported to develop HLH. A retrospective study [38] on 42 children who were diagnosed with post-HSCT HLH suggested that early-onset post-HSCT HLH is a specific entity of HLH. Infections, especially viral infections, were the trigger of HLH in post-transplantation. Etoposide-containing conditioning regimens might reduce the risk of HLH [39].

CONCLUSION

This review covers the recent advances in therapy strategies of HLH. Although the response rates to conventional therapy were different between each subtypes of HLH, HLH-94 is still a reliable protocol of induction treatment. The studies on novel approaches to refractory HLH and different subtypes of HLH will potentially improve outcome of the fatal disease. In the past decade, adult onset HLH has been paid to more and more attention gradually. On account of the heterogeneity of HLH, especially in adult patients, classification of the underlying etiologies of HLH helps to stratify therapy strategies. In future research, individualized therapy is of utmost importance to achieve dramatic improvements in survival. As HSCT is a current ultimate way to prevent HLH from recurrence, more efforts are required to further optimize transplantation protocol. HLH deserves more attention and study.

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Conflicts of interest

There are no conflicts of interest.

Y.W. wrote the review article. Z.W. thoroughly and critically revised the manuscript.

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