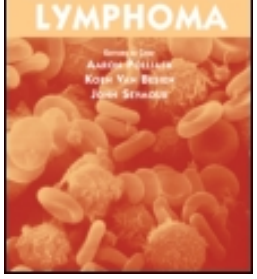

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Management of Severe Neutropenia With Cyclosporin During Initial Treatment of Epstein-Barr Virus-Related Hemophagocytic Lymphohistiocytosis

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Severe neutropenia (absolute neutrophil count <500/μl) is probably due to the combined effects of dysregulated cytokine production and chemotherapeutic agents, and is one of the risk factors in the initial treatment of patients with Epstein-Barr virus-related hemophagocytic lymphohistiocytosis (EBV-HLH). We report here 9 cases of neutropenic HLH, of which 8 were treated with cyclosporin (CSA, 2–6 mg/kg/day; continuous infusion, or 6mg/kg/day; per os, for periods ranging from 9 days to >8 weeks) in the initial neutropenic phase during induction treatment using corticosteroids and etoposide. Five of the 6 cases, in which CSA treatment was started early (before the second week of induction), survived the critical period with recovery of neutrophil counts within a week. The remaining 3 cases, in which CSA was introduced later or not at all, died of infection.

Based on these results, we recommend a prompt short-term CSA infusion during neutropenic episodes in the most common treatment regimen of etoposide and corticosteroids in patients with HLH. Improved neutrophil recovery as a result of CSA treatment makes it possible to continue immunochemotherapy safely and obtain improved patient outcomes.

Keywords: hemophagocytic lymphohistiocytosis, Epstein-Barr virus, neutropenia, cyclosporin A

INTRODUCTION

Development of hemophagocytic lymphohistiocytosis (HLH) (1,2) is triggered by viral or bacterial infection, or associated with lymphoma and other malignancies, and may occur at any age. The terms VAHS (virus-associated hemophagocytic syndrome), IAHS (infection-associated HS) or MAHS (malignancy-associated HS), as well as FHL (familial) or non-familial HLH, are used to indicate the origin of disease. For rapidly deteriorating HLH cases, the most common therapeutic strategy is to administer a combination of etoposide and corticosteroids such as that described by the international protocol HLH-94

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(3). Even with such immunochemotherapy, the event-free survival (EFS) rate of patients with FHL remains approximately 10% at 4yrs.(4), while that of non-familial HLH patients 50–70% (5). One reason for poor therapeutic results is a delay in the initiation of specific management, because differential diagnosis among the different categories of underlying disease can be difficult (2). Other risk factors include familial cases which require hemopoietic stem cell transplantation (4), and fulminant and fatal cases of Epstein-Barr virus (EBV)-related HLH (EBV-HLH) (6–8), for which more effective control measures have recently been reported (9).

Opportunistic infections acquired during neutropenia are a major factor contributing to mortality during the induction phase of treatment for EBV-HLH. The persistent pancytopenia, particularly neutropenia, which has been reported in patients with HLH, may be caused by disease-related cytokine effects as well as the effects of therapy (10–12). Agranulocytosis has been reported to be associated with granular lymphocyte proliferative disorders, mostly those which are T-cell- related (12–15) as well as with Epstein-Barr virus infection (16–22). We previously confirmed that large granular lymphocytosis plays an important role in the pathogenesis of HLH, particularly that of EBV-HLH (23). In such neutropenic conditions in T-cell type granular lymphocyte proliferative disease or EBV-associated HLH, concurrent infections are predominantly bacterial or fungal in origin (11,24,25). Understanding of this pathophysiology in EBV-HLH-related neutropenia may provide new life-saving therapeutic measures. Cyclosporin A (CSA) has been found to be useful in the treatment of macrophage activation syndrome occurring in primary and secondary HLH (26–30) and in chronic neutropenia or immune neutropenia (31,32). We report here prompt improvement of neutropenia as a result of early introduction of CSA during induction treatment for EBV-HLH. This made possible prophylaxis of severe infectious complications with continuation of immunochemotherapy, and resulted in eventual disease control in 5 of 6 cases.

PATIENTS AND METHODS

Clinical features at the onset of EBV-HLH in the 9 cases included in this study are summarized in **Table I**. Diagnosis of HLH was made according to the criteria described by Henter et al. (1,2), and EBV-HLH was diagnosed by serology and by detection of the EBV genome in various biological specimens at the onset of clinical symptoms (9). EBV involvement was confirmed in 8 of the 9 cases and suspected in the remaining case from clinical features including bone marrow findings. None of the cases were familial. Assays of serum ferritin and cytokines were performed as previously described (5).

Patient profiles are summarized in **Table I**; the study group consisted of 5 girls and 4 boys with a median age of 5yr7mo. All cases showed cytopenias of 2–3 lineages, with extremely high serum levels of ferritin, LDH, soluble IL-2 receptor and interferon-gamma. Initial induction treatment and CSA introduction are summarized in **Table II**. Initial treatment protocols were independent in 5 cases (Cases 1–5), while the HLH-94 protocol (3) was employed in the remaining 4 cases; a core combination of corticosteroids (prednisolone, methylprednisolone, or dexamethasone) and VP16 were included in all cases. Granulocyte-colony stimulating factor (G-CSF) was administered in 3 cases. HLH-94 is an international protocol developed by the Histiocyte Society; which consists of an 8-week induction using VP16/dexamethasone (Dexa) followed by maintenance treatment using a combination of VP16/Dexa/CSA for non-resolving cases at the completion of the induction period (3). Severe neutropenia was defined as an absolute neutrophil count (ANC) lower than 500/μl. Treatment response or outcome was evaluated at the end of the induction phase, both for neutropenia (recovered or not) and for clinical improvement of HLH. Improvement of HLH was designated either complete response (CR) or partial response (PR). CR indicates complete resolution of clinical symptoms and signs as well as normalization of laboratory data, particularly serum ferritin levels, which are a good indicator of disease activity. Patients showing persistent fever and other symptoms, or persistent high levels of serum ferritin in spite of the absence of symptoms, were considered to have attained PR. Intensified or maintenance treatment was continued in cases of PR until CR was attained.

TABLE I Patient profiles

Cases	*age/sex*	*disease*	*fever*	*cytopenia*	*liver dysfunction*	*DIC*	*Ferritin*[a] *(ng/ml)*	*LDH*[a] *(IU/l)*	*sIL-2R*[a] *(U/ml)*	*IFN-γ*[a] *(U/ml)*
1	1yr6mo/F	HLH	pos	3[b]	pos	pos	405,500	9,840	29,200	1,240
2	11yr/M	EBV-HLH	pos	3	pos	pos	48,960	6,775	na	na
3	17yr/M	EBV-HLH	pos	2	pos	pos	120,425	8,360	26,400	141
4(#1)	6yr/M	EBV-HLH	pos	2	pos	pos	13,496	2,216	22,700	208
5	12yr2mo/M	EBV-HLH	pos	3	pos	pos	70,000	6,000	39,900	125
6	1yr/F	EBV-HLH	pos	3	pos	pos	78,000	13,755	na	na
7	1yr3mo/F	EBV-HLH	pos	2	pos	pos	35,000	2,000	43,800	440
8	1yr7mo/F	EBV-HLH	pos	2	pos	neg	>3,000	1,623	36,100	234
9	5yr7mo/F	EBV-HLH	pos	2	pos	pos	10,222	6,040	8,180	226

In Case 1, involvement of EBV was suspected, but not confirmed.
a. normal ranges are: ferritin (8–78 ng/ml), LCH (234–471 IU/l), sIL-2R (<1,090 U/ml) and IFN- γ (<1.0 U/ml)
b. number of lineages involved, pos : positive, neg: negative, na: not available

TABLE II Induction treatment for HLH with or without early introduction of CSA

Cases	*treatment*	*CSA beginning*	*doses*	*duration*
1	VP16/Cs/G-CSF	none	0	none
2	VP16/Cs	wk 1	5mg/kg/d, drip	2 weeks
3	ET/VP16/G-CSF	wk 4	3mg/kg/d, drip	2 weeks
4(#1)	VP16/Cs	wk 3	3mg/kg/d, drip	1.5 weeks
(#2)	VP16/Cs	wk 2	3mg/kg/d, drip	3 weeks
5	VP16/Cs	wk 1	2mg/kg/d, drip	>8 weeks
6	VP16/Cs	wk 2	6mg/kg/d, drip	>4 weeks
7	ET/VP16/Cs	wk 2	3mg/kg/d, drip	2 weeks
8	VP16/Cs	wk 0	1.6mg/kg/d, drip	9 days
9	VP16/Cs/G-CSF	wk 2	6mg/kg/d, po	2 weeks

Cs: corticosteroids, G-CSF: recombinant granulocyte-colony-stimulating factor; ET: exchange transfusion, po: per os

RESULTS

Disease outcomes and changes in ANC are summarized in **Table III**. On admission, 7 of the 9 cases already had neutropenia (<1,000/μl) **(Table III)** and all cases received corticosteroids and VP16 as an initial regimen and 3 received G-CSF as well (**Table II**). The effect of CSA, which was administered by continuous infusion (1.6–6 mg/kg/day) except in one case(6mg/kg/day, orally), was evaluated in 9 courses in 8 patients (Case 4 was treated twice for neutropenic episodes with CSA). As shown in **Table II**, CSA was introduced early (week 0-week 2) in 7 episodes, and later (week 3-week 4) in 2 episodes. The duration of CSA treatment ranged from 9 days to longer than 8 weeks. By week 2 of induction treatment, 8 of the 9 cases displayed severe neutropenia (<500/μl), whereupon VP16 was stopped in some, but not in all cases. In those cases in which ANCs returned to levels above 1,000/μl following CSA administration, reinstitution of a combination of corticosteroid and VP 16 therapy became possible and all of these cases subse-

quently showed favorable responses. Five of the 8 cases treated with CSA showed recovery; three of these cases attained CR and two showed PR. Case 1 died without CSA rescue. Case 2 displayed extremely hypocellular bone marrow, did not respond to CSA regardless of very early introduction and died of MRSA sepsis. Case 3 was unresponsive to late rescue by CSA and died of aspergillosis. Over the period during which CSA was administered, no adverse reactions were noted. Representative treatment courses are illustrated in **Fig. 1**, and two cases in which favorable outcomes were obtained are briefly described below.

CASE REPORTS

Case 5

A 12 year-old boy presented with persistent fever, cytopenia (ANC 44/μl, platelet count 24,000/μl), hepatomegaly (7cm), splenomegaly (8cm), jaundice (total bilirubin 11.3mg/dl), coagulopathy and cervical adenopathy in April 1997. He was initially treated with exchange transfusion (ET), followed by VP16 (100–150mg/day. IV) for 5 days and prednisolone (PSL, 60mg/day. per os). A week later because of persistent severe cytopenia (ANC 80/μl, Hb 8.7g/dl, PLTS 15, 000/μl), CSA (2.0mg/kg, continuous infusion, daily) and dexamethasone (Dexa, 10mg/day, continuous infusion) were introduced; this treatment completely rescued hemopoiesis in 10 days. Thereafter, the patient was treated according to the HLH-94 protocol (3). Serum ferritin was reduced from 14,500ng/ml initially to 1,000ng/ml. but remained abnormally high at the end of 2 months treatment. Thereafter, this patient's disease has been well controlled with the maintenance protocol of HLH-94. **(Fig 1c)**.

Case 7

A 1 year 3 month-old girl presented with fever, cytopenia (ANC 689/μl, Hb 8.7g/dl, platelet count 28,000/μl), hepatomegaly (5 cm), no splenomegaly, coagulopathy, and with generalized edema in January 1997. Soon after exchange transfusion (ET), treatment according to the HLH-94 protocol (3) was begun. Although the response was rapid, progression of neutropenia (nadir 34/μl) necessitated interruption of VP16 administration, so that the patient was treated with CSA (2mg/kg/day, continuous infusion) alone for 2 weeks. At the point of hemopoietic recovery, the patient was replaced on the HLH-94 induction regimen and thereafter showed good response to the maintenance protocol. **(Fig 1b)**

DISCUSSION

HLH is a disease of uncontrolled, dysregulated cellular immune reaction, in which abnormally regulated T-cell activation leads to secondary macrophage activation (23,33). This abnormal immune response is induced by various triggering factors such as viral or bacterial infections or specific types of lymphoma. The pathophysiology of this condition is associated with an increase in the levels of both T-cell-derived and macrophage-derived cytokines, particularly TNF-α and IFN-γ(34,35). It has been shown that proliferation of granular lymphocytes is closely related to the pathogenesis of HLH (23). In addition, the impact of hypercytokinemia was previously reported as a factor influencing patient prognosis (34–37). In these studies, levels of serum IL-1 β and TNF-α, IFN- γ, and sIL-2 receptor were shown to have a significant prognostic correlation.

Particularly in EBV-related diseases, these cytokines exert myelosuppressive effects causing neutropenia (11,16–22) Recently, Larochelle et al. (38) showed that EBV actually penetrates and causes apoptosis in neutrophils. We have found a significant inverse correlation between serum concentrations of IFN-γ and white blood cell counts in HLH patients (unpublished data). Moreover, at the onset of disease in 70 cases of childhood HLH, 22 cases (31.4%) had severe (ANC <500/μl) and 18 cases (25.7%) had mild (ANC 500–999/μl) neutropenia; of these severe cases, half were EBV-associated (our unpublished observations). Even in these situations, neutropenia often escapes a physician's attention if there are white blood cell counts above 1,000/μl.

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