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Assessment of immunochemotherapy and stem cell transplantation on EBV-associated hemophagocytic lymphohistiocytosis in children: a systematic review and meta analysis

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Abstract. – *Background and Objectives:* **Although immunochemotherapy had been reported to be effective initial treatment for patients with Epstein Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH), and stem cell transplantation (SCT) was employed for patients with refractory disease, the long-term outcome of these patients underwent such treatment remained uncertain. The main purpose of this study was to make a primary system review on the outcome of EBV-HLH patients treated with immunochemotherapy and/or SCT.**

Material and Methods: **A system review and meta analysis was conducted on studies which collected from published PubMed and China Knowledge Resource Integrated Database (CNKI). The analysis was based on clinical characteristics and follow-up. Search strategy and selection criteria were identified by relevant articles, the period was defined from January1990 to October 2010. Search terms included all relevant terms. English and Chinese language papers were reviewed.**

Results: **A total of 11 articles include 342 EBV-HLH patients that were identified with our search terms fulfilled the eligibility criteria. Overall 104/342 patients (30.4%) died at the end of respective study. In 288 patients who did not receive SCT, 93/288 patients (32.3%) patients died. While in 54 patients who underwent SCT, 11/54 patients (20.4%) died at the end of respective study. Four articles had the contents both of immunochemotherapy and SCT. When using a meta analysis compared the mortality between immunochemotherapy and SCT groups, there was no statistical significance could be found, the Odds Ratio is 1.10 (0.43~2.84), (p = 0.84).When compared the mortality between SCT group and total EBV-HLH patients, there was still no statistical significance could be found, the Odds Ratio is 0.99 (0.39~2.53), (p = 0.98).**

Conclusion: **Etoposide-containing immunochemotherapy and SCT both decreased the mortality in EBV-HLH patients in the past decade. There was not enough evidence to suggest that SCT is better than immunochemotherapy in children with EBV-HLH. And such result may justify further research.**

Key Words:

Epstein-Barr virus, Hemophagocytic lymphohistiocytosis, Hematopoietic stem cell transplantation, Meta analysis.

Introduction

Epstein-Barr virus (EBV), also called human herpesvirus 4 (HHV-4), was one of the most common viruses, infecting over 90% of humans and persisting lifelong[1]. EBV was the major triggering factor producing hemophagocytic lymphohistiocytosis (HLH) in children, called EBV associated hemophagocytic lymphohistiocytosis (EBV-HLH). The clinical features of EBV-HLH were typically included of high fever, cytopenia, liver dysfunction and coagulopathy, similar to other types of HLH defined by Henter and Imashuku[2,3]. HLH comprised primary (familial or hereditary, FHL) and secondary HLH[4]. Patients with FHL had a very poor prognosis and their only hope of cure is undergoing a hematopoietic stem cell transplantation (SCT). By contrast, EBV-HLH was generally considered to be a secondary HLH, although the differential diagnosis from FHL or X-linked lymphoproliferative disease (XLP) must be done before further treatment[5].

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The prognosis of EBV-HLH had been assumed to be better than that of FHL. However, unless optimal treatment was rapidly carried out, the outcome of EBV-HLH was also poor[3]. Thus, allogeneic SCT which consistently induces disease resolution and seemed to be curative in many cases, had been suggested as the choice for treatment on EBV-HLH[6], although it was also associated with high mortality. However, because of the complicated pathogenesis and limited number of patients, large study conducted in single-center on the long-term outcome of EBV-HLH patients was not available. The present study was designed using a meta analysis method, to make a primary system review on the different outcome of EBV-HLH patients treated with immunochemotherapy or SCT in children.

Materials and Methods

A PubMed software was used to search Medline and China Knowledge Resource Integrated Database (CNKI) (Library of the Capital Medicine University, Beijing, China) using the following search terms and relative Chinese words: "hemophagocytic syndrome", "haemophagocytic syndrome", "hemophagocytosis", "haemophagocytosis", "histiocytic hemophagocytosis", "histiocytic haemophagocytosis", "hemophagocytic lymphohistiocytosis", "haemophagocytic lymphohistiocytosis", "histiocytosis", "Epstein barr virus", "herpesvirus, human", "EBV and HLH" for studies listed between January 1990 and October 2010. Eligibility criteria for inclusion were (1) studies must have ascertained EBV status of HLH in child (aged 0~18 years), and (2) studies had to report the life status after immunochemotherapy or SCT or provide enough information to calculate this estimate. (3) Studies had made differential diagnosis of FHL or X-linked lymphoproliferative disease (XLP) from EBV-HLH. Case report and studies only reported FHL were excluded.

A total of 185 papers were identified by their titles and whole contents reviewed for relevance. Only 11 studies met the inclusion criteria[7-17]. The following data were abstracted as available: first author, year of publication, study period, sample size, EBV-HLH prevalence, main therapeutic regiments, sex ratio, age range, life status at the end of respective study.

Statistical Analysis

Meta-analysis was performed with Review Manager 5 (RevMan 5, Cochrane Information Management System team at www.cc-ims.net/RevMan). An effect size for each of the studies we analyzed was calculated by an Odd's ratio (OR) or the weighted mean difference (WMD) according to the Review Manager 5. The decision to use one statistical method over the other depended on whether the measured event was dichotomous or continuous, whereas the choice to use a random or fixed effect model for analysis depended on Q statistics. p values less than 0.05 were considered statistically significant.

Meta-analytic assumptions were assessed with Egger test ("metabias") of funnel plot asymmetry (publication bias).

Results

A total of 11 articles include 342 EBV-HLH patients that were identified with our search terms concerned of immunochemotherapy and/or SCT on EBV-HLH patients fulfilled the eligibility criteria. The earliest study was published in 1999[17] and the most recent studies in 2010[7,8]. The largest study included 81 EBV-HLH cases[15], and the smallest included 4 EBV-HLH cases[17]. Five of these studies were conducted in single-center[8-10,12,13]. The analysis was based on life status at the end of the respective study (Table I).

In 10 articles, the number of female: male patient was 180: 134; the sex ratio could not find in one article[9]. The description of age distribution varied in each article, and we could not calculate an overall median age in all of the articles. Most of them were around four to five years old.

Overall 104/342 patients (30.4%) died at the end of respective study. 54 patients underwent SCT, one of whom underwent a consecutive transplantation. In 288 patients (among them 264 patients received etoposide-containing regimens) who did not receive SCT, 93/288 patients (32.3%) patients died at the end of respective study. While in 54 patients who underwent SCT, 11/54 patients (20.4%) died at the end of respective investigation (Table II).

Four articles had the contents both of immunochemotherapy and SCT. When using a meta analysis compared the mortality between immunochemotherapy and SCT groups, there was

Table I. Main characteristics of 10 studies concerned of treatment in EBV-HLH.

First author	Published year	Study period	Patients number			Main chemotherapy regiments	Source of patients	EBV-HLH patients	
			Total	EBV-HLH	SCT in EBV-HLH			Gender (F/M)	Median age at onset or diagnosis
Ohga et al[7]	2010	1995-2005	57	14	15	Combination of corticosteroid, CSA, and VP16	Multi-center	10:4	5.5 y (6 m-18 y)
JIN et al[8]	2010	2003-2008	78	78	0	HLH-94 or HLH-04 (60%)	Single-center	31:47	4 y (6 m-14 y)
Lee WI et al[9]	2009	1992-2007	32	12	0	IVIG, steroids, CSA, and VP16	Single-center	?	2 m-15.5 y (5.0 y ± 9.8 m)
Beutel et al[10]	2009	2003-2007	12	8	1	IVIG, steroids, VP-16, CSA	Single-center	6:2	5 y 6 m (12 m-13 y 8 m)
Sato et al[11]	2008	1997-2003	74	10	10	12 GyTBI/VP16/CY 3 (30%) u/VP16/CY 4 (40%)	Multi-center	9:1	5.0 y (1 y-51 y)
Yang et al[12]	2007	2003-2006	26	26	0	HLH-04 19 (71.1%)	Single-center	2:3	25.5 m (4 m-13 y)
Lee JS et al[13]	2005	2001-2004	4	4	0	Steroids and VP-16	Single-center	2:2	5.2 y (2.3-13.0)
Imashuku et al[14]	2004	1992-2001	78	78	12	VP-16 containing regimens (85%)	Multi-center	49:29	< 2 y 37.2%, 2-15 y 56.4%, > 15 y, 6.4%
Imashuku et al[15]	2002	1992-1999	81	81	9	Individual protocols 22 (27.2%) HLH-94 59 (72.8%)	Multi-center	52:29	4 y (2 m to 33 y)
Imashuku et al[16]	2000	1986-1997	32	27	4	Steroids and VP-16 17 (53%)	Multi-center	16:16	< 2 y, 37.5%, 2-14 y 53.1%, > 14 y, 9.4%
Imashuku et al[17]	1999	1988-1998	17	4	4	VP-16, CSA	Multi-center	3:1	1 y 3 m-7 y

TBI, total body irradiation; VP16, etoposide; CY, cyclophosphamide; Bu, busulfan. CSA, cyclosporine A.IVIG, intravenous immunoglobulin.

Table II. Clinical outcome of EBV-HLH patients in the studies.

First author	Status at the end of study: Alive SCT	Alive non-SCT	Dead SCT	Dead non-SCT	Prognosis
Ohga et al	12	/	2	/	10-year OS rates (median ± SE%) 85.7 ± 9.4%
JIN et al	/	29	/	38	No follow-up data were available for 11 patients
Lee WI et al	/	6	/	6	Can not gain
Beutel et al	1	7	0	0	All alive at the end of study
Sato et al	7	/	3	/	Event-free survival rate , 0.614 ± 0.186
Yang et al	/	0	/	9	52.6% are alive at the end of study
Lee JS et al	/	4	/	0	Complete remission period 15-27 m (median, 19 m)
Imashuku et al	9	50	3	16	59 (75.6%) are alive at the end of study
Imashuku et al	6	47	3	15	Can not gain
Imashuku et al	4	14	0	9	Overall survival at 3 years 53%
Imashuku et al	4	/	0	/	Duration of post SCT remission 3.5 m^+~41 m^+

no statistical significance could be found, the Odd's Ratio is 1.10 (0.43~2.84), $p = 0.84$ (Figure 1). When using a meta analysis compared the mortality between SCT group and total EBV-HLH patients, there was still no statistical significance, the Odd's Ratio is 0.99 (0.39~2.53), $p = 0.98$ (Figure 2).

The heterogeneity was also calculated measures of the Chi^2 and I^2 statistics, this test identified no evidence of publication bias ($p = 0.42$ and $p = 0.46$, respectively), indicate that the studies have good heterogeneity. The publication bias was created by funnel plots, as Figures 3 and 4. Although there seemed no obvious publication bias, a funnel plot was not usually created for such a small number of studies. More information was needed for further reseach.

Discussion

EBV-related severe diseases, such as EBV-HLH, were more prevalent in the East Asian population. The reason for this was still unknown. EBV-HLH posed unusual challenges to pediatric physician and hematologists. It may be difficult to distinguish from infectious mononucleosis (IM), chronic active EBV infection (CAEBV), septicemia, certain hematological malignancies, and systemic autoimmune disorders. Sometimes therapy should be started when there is a strong clinical suspicion of HLH, although the patient may not necessarily fulfill all the diagnostic criteria[13]. But this opinion was still controversial. Belyea et al[18] reported two patients with EBV-HLH who experienced sponta-

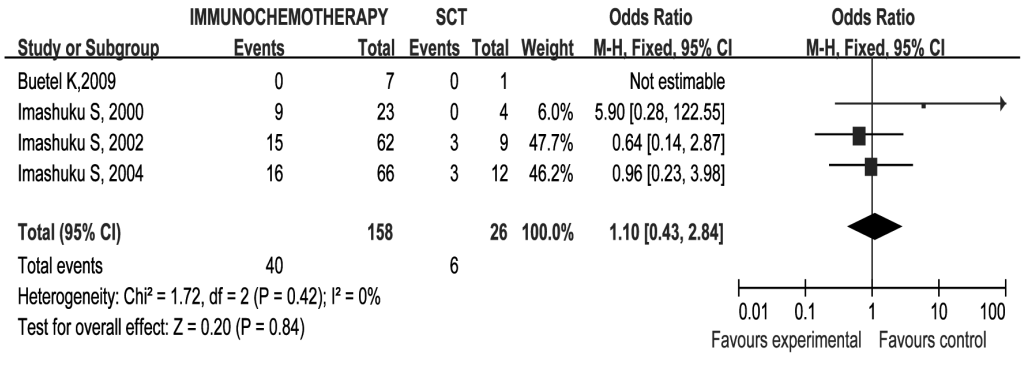

Figure 1. Life status at the end of respective study between immunochemotherapy and SCT.

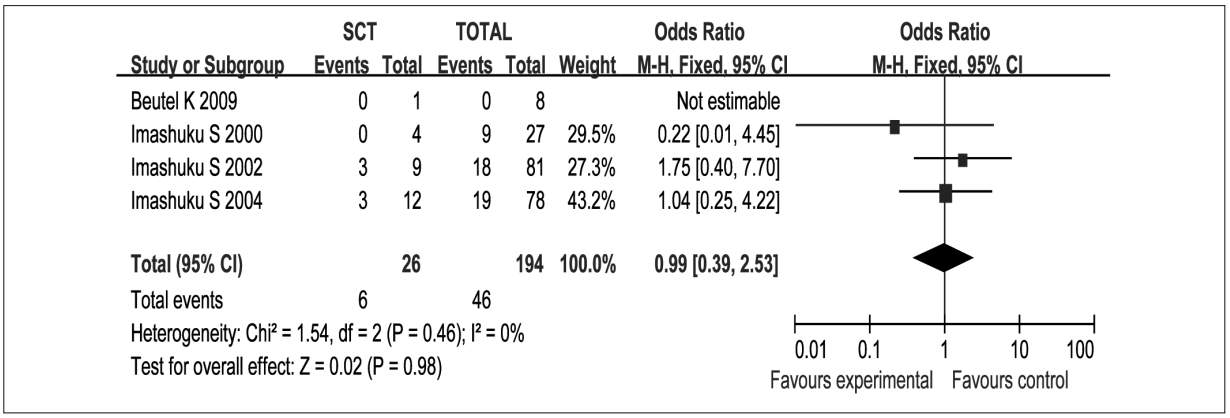

Figure 2. Life status at the end of respective study between SCT and total EBV-HLH patients.

neous resolution prior to the initiation of immunochemotherapy, suggesting that there may be a subgroup of patients with EBV-HLH who do not need a potentially toxic therapies. Then the next problem was: whether or not shall an EBV-HLH patient undergo SCT at the early stage?

However, because most EBV-HLH patients were East Asian origin and the number of patients was limited, comparison of treatment outcomes for large cohorts of single-center patients with EBV-HLH was very difficult. The present report conducted system review and a meta-analysis of the published literature to estimate the difference outcome of EBV-HLH patients treated with immunochemotherapy and/or SCT. Most of the studies came from Japan. In one of the largest study[14], the Author said it include two previous investigations[19,20], we carefully excluded them out of our study. Before this research, few studies concerned the population of Chinese mainland were found at PubMed, the reason maybe for the language barrier. This report also included two Chinese studies published in recent years, we hope it would be helpful for a better comprehension to EBV-HLH.

The results of this system review analysis indicate that the overall mortality decreased in the past decade by immunochemotherapy and/or SCT, compared to clinical outcomes reported by Chen et al[21] and by Imashuku et al[22] for children with secondary HLH (40.9%±10.5% and 57.2%±6.2%, respectively). Overall 104/342 patients (30.4%) died at the end of respective investigation. But this still was a very high mortality compared to other non-malignant diseases in children. Especially in developing countries[23].

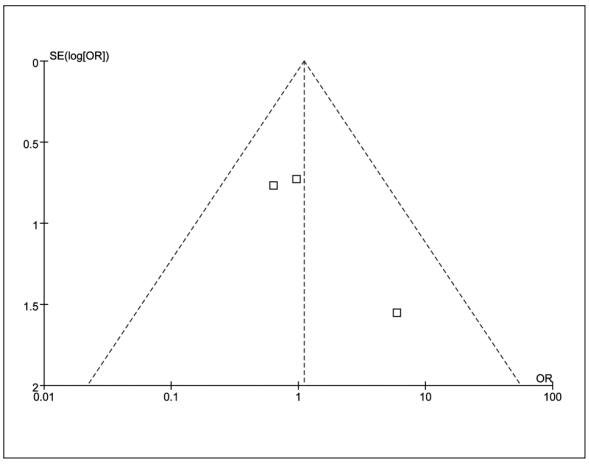

Figure 3. The publication bias of the 4 studies when compared between immunochemotherapy and SCT.

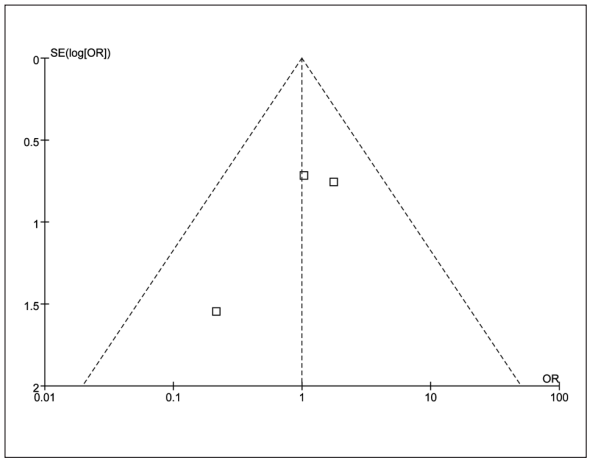

Figure 4. The publication bias of the 4 studies when compared between SCT and total EBV-HLH patients.

Imashuku et al[20] suggested that prompt use of etoposide containing regimens (4 weeks from diagnosis) was a critical factor in successful therapy for EBV-HLH. Additionally, higher doses of etoposide during the first 4 weeks of treatment was linked with better prognosis. But the complication of etoposide-induced neutropenia[24], together with etoposide-related acute myeloid leukemia (AML)[25], would contribute to the high mortality too. The hypercytokinemia that derived from abnormal activation of macrophages and T/NK cells was the main cause of death in EBV-HLH patients. This cytokine storm could result in multiple organ failure (MOF, e.g. cardiac, pulmonary, hepatic and renal), as well as severe hemorrhage (especially in the central nerve system). It could also result in immune deficiencies that promote secondary opportunistic infections. In this sense, the initial treatment of EBV-HLH should be similar to the treatment of systemic inflammatory response syndrome (SIRS)[26]. Once the acute cytokine storm was under control, the proliferating EBV^+ T/NK cells could be eradicated. This can be achieved by treatment with etoposide and other therapeutic agents.

The EBV-HLH spectrum ranged from mild (low-risk) to severe (high-risk) disease, and the therapy applied must be adjusted to the grade of disease severity. SCT was mandatory in the treatment of XLP and FHL patients[27] and was the treatment of choice for refractory cases of EBV-HLH[17] as well as for CAEBV[28]. SCT was beneficial and could lead to a cure in XLP and FHL cases was well established. However, EBV-HLH and CAEBV were usually not immediately considered to be malignant diseases like leukemia, and considered the severe complications of SCT, proceeding to SCT should be well considered. In this review, 54 patients underwent SCT, one of whom underwent a consecutive transplantation. 11/54 patients (20.4%) died at the end of respective study, compared to 93/288 (32.3%) patients who did not underwent SCT died at the end of respective study. But this result could not indicate that SCT was better than immunochemotherapy. The reasons maybe as the follows: first, there were some patients did not underwent regular immunochemotherapy or supportive therapy because of the economic reason (especially in developing countries); the second reason may contribute to the early death of some patients (especially in infant child), who did not have a chance to undergo a SCT; the last reason may contribute to the special genetic background that different from the gene mutation known in FHL patients, SCT would do benefit to such patients.

Further research by using a meta analysis in present research indicated that there was no statistical significance between patients treated with immunochemotherapy and SCT. In the 4 articles both concerned of immunochemotherapy and SCT, whether the compare between the immunochemotherapy group and SCT group or the compare between SCT group and total patients in respective studies, the Odd's ratio was 1.10 and 0.99 respectively, $p > 0.05$. In addition, for limitation of the 4 studies, the meta analysis results of our study needed more information in the future research.

In conclusion, etoposide-containing immunochemotherapy and SCT both decreased the mortality in EBV-HLH patients in the past decade. But there was still high mortality in them. Further study should pay more attention on the pathogenesis and possible genetic background in such patients, for the present study could not give enough evidence to suggest that SCT was better than immunochemotherapy in children with EBV-HLH.

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