Annals of Hematology (2022) 101:2289–2296
https://doi.org/10.1007/s00277-022-04953-1

ORIGINAL ARTICLE

Clinical characteristics and treatment of NK/T-cell lymphoma–associated HLH

Guangqiang Meng[1] · Jingshi Wang[1] · Tingting Cui[1] · Zhao Wang[1]

Received: 20 April 2022 / Accepted: 30 July 2022 / Published online: 24 August 2022

Abstract

Natural killer (NK)/T-cell lymphoma–associated hemophagocytic lymphohistiocytosis (NK/T-LAHLH) is a rare and life-threatening disorder. Its clinical characteristics and appropriate treatment options are unclear. This study aimed to investigate the clinical characteristics and treatment options for this disease. We retrospectively analyzed the clinical data of 84 patients with NK/T-cell lymphoma and compared the characteristics, treatment, and survival between patients with and without HLH. Patients in the NK/T-LAHLH group were more likely to be younger age and have hepatosplenomegaly, B symptoms, neutropenia, anemia, thrombocytopenia, elevated lactate dehydrogenase levels, reduced serum albumin levels, bone marrow involvement, Ann Arbor stage III/IV, and International Prognostic Index score ≥ 3. After multivariate analysis, it was found that elevated lactate dehydrogenase and Ann Arbor stage III/IV were risk factors for HLH in patients with NK/T-cell lymphoma. After 2 weeks of therapy, 78.6% (11/14) patients who received the L-DEP/DEP regimen achieved an overall response rate of HLH, which was higher than that in 42.9% (9/21) patients who received the VP-16 + dexamethasone-based regimen. NK/T-LAHLH patients had poorer survival than non-HLH-NK/TCL patients. For NK/T-LAHLH, the L-DEP/DEP regimen may have a better response rate than the VP-16 + dexamethasone-based regimens.

Keywords NK · T-cell lymphoma · Hemophagocytic lymphohistiocytosis · Treatment

Introduction

Natural killer (NK)/T-cell lymphoma–associated (NK/T-LA) hemophagocytic lymphohistiocytosis (HLH) (NK/T-LAHLH) is a life-threatening disease characterized by the hypersecretion of inflammatory cytokines induced by macrophage hyperactivation. Hypercytokinemia and uncontrolled immune activation result in clinical manifestations and laboratory findings of HLH such as fever, pancytopenia, hepatosplenomegaly, hyperferritinemia, coagulopathy, liver dysfunction, and hemophagocytosis in the bone marrow [1, 2]. HLH can be classified into primary and secondary types. Secondary HLH is associated with infection, malignant tumors, autoimmune diseases, and other causes. Rivière et al. found that, among the causes of HLH, hematological malignancies, especially non-Hodgkin's lymphoma, accounted for 56% of the cases [3]. Moreover, NK/T-LAHLH cases account for 35% of all LAHLH cases, making it among the most common type of LAHLH, especially in Asia [4].

The Epstein-Barr virus (EBV), the most common cause of infection-induced HLH, has a high mortality rate. In cases of EBV-positive LAHLH, EBV and lymphoma jointly participate in the occurrence and progression of HLH [5, 6]. More than 90% of NK/T-cell lymphoma cases are EBV positive, which may explain why NK/T-LAHLH is a common LAHLH. This also explains why NK/T-LAHLH has a poor prognosis. For example, Takahashi et al. reported that patients with NK/mature T-cell lymphoma–associated HLH had a poor prognosis, with a median survival time of 1–2 months [7]. Ishii et al. conducted a retrospective study of 567 HLH patients and found that, among HLH patients,

✉ Zhao Wang
wangzhao@ccmu.edu.cn

Guangqiang Meng
menggq2001@163.com

Jingshi Wang
wangjingshi987@126.com

Tingting Cui
cttdyx111@126.com

[1] Department of Hematology, Beijing Friendship Hospital, Capital Medical University, YongAn Road 95th Xicheng District, Beijing 100050, China

NK/T-LAHLH patients had the worst prognosis, with a 5-year survival rate of < 15% [8].

Due to the poor prognosis and few investigations of a large sample size of NK/T-LAHLH, no standard effective treatment regimen is available. In this retrospective study, we reviewed 48 patients with NK/T-LAHLH and 36 patients with NK/T-cell lymphoma to better understand the clinical characteristics and treatment of NK/T-LAHLH.

Methods

Patients

Between June 2013 and September 2019, 84 patients were diagnosed with NK/T-cell lymphoma and 48 patients were diagnosed with NK/T-LAHLH at our Hospital. The inclusion criteria for patients were as follows: (1) histopathological diagnosis of NK/T-cell lymphoma and (2) fulfillment of the 2004 diagnostic criteria for NK/T-LAHLH [1]. Follow-up was continued up through March 2020, until the last follow-up or the patient's death.

Laboratory findings

All patients underwent a comprehensive physical examination. Laboratory tests included tests for complete blood count, kidney and liver function, lactate dehydrogenase (LDH), coagulation function, serum ferritin, peripheral blood mononuclear cells (PBMCs), plasma EBV DNA, and EBV-encoded early small RNA (EBER) as well as bone marrow smear and biopsy. Before 2015, our hospital performed only peripheral blood EBV DNA testing; thereafter, plasma EBV DNA testing became available. EBV DNA imaging examinations included positron emission tomography/computed tomography (CT) or cervical, chest, abdominal, and pelvic CT; abdominal ultrasonography including the liver, gallbladder, pancreas, spleen, and kidney; and superficial lymph node ultrasonography. For HLH patients, soluble CD25 (sCD25) levels and NK cell activity levels were tested. Serum amylase was detected before and after the asparaginase.

Clinical staging and treatment response evaluation

Lymphoma was staged using the Ann Arbor staging system. Risk stratification was defined based on International Prognostic Index (IPI) scores. The response criteria of Cheson et al. were used to evaluate treatment response as complete remission (CR), partial remission (PR), stable disease, or progressive disease [9]. The response to HLH treatment was assessed according to the revised United States HLH Cooperative Group efficacy criteria as CR, PR, or no response [10]. Overall response rate (ORR) was defined as PR and CR.

Treatment of HLH

The HLH-1994 regimen was as follows: VP-16 dose, 150 mg/m^2 (50–75 mg/m^2 for patients aged > 40 years, 75–100 mg/m^2 for patients aged 15–39 years, and 75–150 mg/m^2 for patients aged < 15 years) and dexamethasone dose, 10 mg/m^2/day in weeks 1–2, 5 mg/m^2/day in weeks 3–4, 2.5 mg/m^2/day in weeks 5–6, 1.25 mg/m^2/day in week 7, and dose reduction until discontinuation in week 8. In the HLH-04 regimen, cyclosporine (6 mg/kg/day) was applied simultaneously with VP-16 in advance. The DEP regimen was as follows: liposomal doxorubicin dose, 25 mg/m^2/day on day 1; VP-16, 100 mg/m^2/day on day 1; and methylprednisolone dose, 2 mg/kg/day on days 1–3, 0.75 mg/kg/day on days 4–7, 0.25 mg/kg/day on days 8–10, and 0.1 mg/kg/day until the next cycle. The dose of pegaspargase was 1500–2000 U/m^2 on day 3 or days 4 and 5.

Patients were monitored for drug-related adverse reactions during treatment, such as coagulation abnormalities and serum amylase elevation secondary to asparaginase, as well as cardiac adverse events secondary to Liposomal doxorubicin. Appropriate treatment should be given for the above adverse events, and the drugs should be discontinued if necessary.

Statistical analysis

Statistical analysis was performed using SPSS version 18.0. Normal distribution data are represented by $x \pm SD$, and non-normally distributed data are presented as median and extreme values. The *t*-test or rank-sum test was used to examine quantitative data, while the $\chi 2$ test and Fisher's exact probability test were used to compare qualitative data. Multivariate analysis was used by logistic regression. The Kaplan–Meier method was used to estimate overall survival (OS), defined as the time from the date of diagnosis to the date of death from any cause, last follow-up, or follow-up loss. Survival rates were compared using log-rank tests. All *P* values were two sided, and statistical differences were determined at a level of $P < 0.05$.

Results

Comparison of clinical and laboratory characteristics between patients with and without HLH

The clinical characteristics and laboratory findings of all 84 patients are shown in Table 1. Patients in the NK/T-LAHLH group were more likely to be younger age and

Table 1 Clinical characteristics in NK/T-LAHLH and non-HLH-NK/T-CTL groups

Characteristics	NK/T-LAHLH group $n=48$ (%)	Non-HLH-NK/T-CTL group $n=36$ (%)	*P* value
Gender			
Male	31 (64.6%)	24 (66.7%)	0.901
Female	17 (35.4%)	12 (33.3%)	
Age (years), mean ± SD	35.56 ± 14.54	46.78 ± 16.76	0.002
Ann Arbor stage			
I/II	3 (6.2%)	29 (80.6%)	< 0.001
III/IV	45 (93.8%)	7 (19.4%)	
B symptoms			
Yes	48 (100%)	14 (38.9%)	< 0.001
No	0	22 (61.1%)	
IPI score			
< 3	15 (31.2%)	35 (97.2%)	< 0.001
≥ 3	33 (68.8%)	1 (2.8%)	
EBER positive			
Yes	47 (97.9%)	34 (94.4%)	0.799
No	1 (2.1%)	2 (5.6%)	
BM involvement			
Yes	21 (43.8%)	1 (2.8%)	< 0.001
No	27 (56.2%)	35 (97.2%)	
Neutropenia (%)	20 (41.7%)	1 (2.8%)	< 0.001
Anemia (%)	26 (54.2%)	2 (5.6%)	< 0.001
Thrombocytopenia (%)	40 (83.3%)	1 (2.8%)	< 0.001
LDH > 240 U/L (%)	41 (85.4%)	13 (36.1%)	< 0.001
Serum albumin reduced (%)	36 (75.0%)	9 (25.0%)	< 0.001
Hepatosplenomegaly	34 (70.8%)	6 (16.7%)	< 0.001

NK/T-LAHLH, NK/T-cell lymphoma–associated hemophagocytic lymphohistiocytosis; *SD*, standard deviation; *B*,

symptoms fever, drenching night sweats, and weight loss > 10%; *IPI*, score International Prognostic Index; *EBER*, Epstein-Barr virus-encoded early small RNA; *BM*, bone marrow; *LDH*, lactate dehydrogenase

have hepatosplenomegaly B symptoms, neutropenia, anemia, thrombocytopenia, elevated LDH levels, reduced serum albumin levels, bone marrow involvement, Ann Arbor stage III/IV, and IPI scores ≥ 3 ($P < 0.05$). Among the 48 NK/T-LAHLH patients, 42 (87.5%) patients had HLH at the time of initial diagnosis, while six (12.5%) patients developed HLH as the lymphoma progressed. The baseline characteristics of NK/T-LAHLH patients in terms of HLH are shown in Table 2.

Comparison of variables between patients in the L-DEP and VP-16 + dexamethasone-based groups

The clinical characteristics of patients with NK/T-LAHLH are summarized in Tables 3 and 4. The white blood cell count in the L-DEP/DEP group were significantly higher than those in the VP-16 + dexamethasone-based group ($P = 0.001$). However, the EBV DNA load of PBMCs in the VP-16 + dexamethasone-based group was higher than that in the L-DEP group ($P = 0.010$). There were no statistically significant intergroup differences in other clinical indicators ($P > 0.05$).

Treatment outcomes and survival analysis

Of the 48 patients with NK/T-LAHLH, 47 patients received initial induction therapy for HLH. Twelve patients underwent the L-DEP regimen, and two patients were treated with the DEP regimen. Twenty-one patients received VP-16 + dexamethasone-based regimens (HLH-94 regimen, 16 patients; HLH-04 regimen, three patients; VP-16 and dexamethasone, two patients). Nine patients received ECHOP or ECHOP-like regimens. Two patients received only glucocorticoids as the main therapy. One patient received an L-GDP regimen. After 2 weeks of induction therapy, none of the patients achieved CR. Of the 14 patients who underwent the L-DEP/DEP regimen,

Table 2 Baseline characteristics of patients of NK/T-LAHLH

Characteristics	*N* (%)/mean ± SD
Gender	
Male	31 (64.58%)
Female	17 (35.42%)
Age (years), mean ± SD	35.56 ± 14.51
Fever	48 (100%)
Hepatosplenomegaly	34 (70.83%)
Hemophagocytosis in bone marrow	41 (85.42%)
Cytopenia for at least two cell lines	12 (25%)
Laboratory data, mean ± SD	
ANC ($\times 10^9$/L) (1.8–6.3 $\times 10^9$/L)	1.59 ± 1.49
Hb (g/L) (130–175 g/L)	93.11 ± 23.81
PLT ($\times 10^9$/L) (125–350 $\times 10^9$/L)	62.83 ± 67.48
ALT (U/L) (9–50 U/L)	143.89 ± 125.18
AST (U/L) (15–40 U/L)	157.40 ± 133.85
ALB (g/L) (40–55 g/L)	29.56 ± 5.41
TBIL (μmol/L) (3.42–17.10 μmol/L)	74.81 ± 88.87
LDH (U/L) (120–250 U/L)	784.44 ± 515.11
FIB (g/L) (2–4 g/L)	4.73 ± 21.60
TG (mmol/L) (0.57–1.70 mmol/L)	3.19 ± 1.77
Ferritin (μg/L) (24.00–336.00 μg/L)	7979.25 ± 13,916.93
sCD25 (pg/mL) (< 6400 pg/mL)	28,981.58 ± 12,962.68
NK cell function (depressed)	22 (45.83%)

Abbreviations: *SD*, standard deviation; *ANC*, absolute neutrophil count; *Hb*, hemoglobin; *PLT*, platelets; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *ALB*, albumin; *TBIL*, total bilirubin; *LDH*, lactate dehydrogenase; *FIB*, fibrinogen; *TG*, triglycerides; *NK*, natural killer

11 (78.6%) patients achieved PR. Of the 12 patients who received the L-DEP regimen, 10 (83.3%) achieved PR. Of the 21 patients who received VP-16 + dexamethasone-based regimens, nine (42.9%) patients achieved PR. Of the eight patients who received an ECHOP or ECHOP-like regimen, six patients were available for evaluation at 2 weeks, of whom two (33.3%) patients achieved PR. The 2-week ORR of patients in the L-DEP/DEP regimen group was higher than that of patients in the VP-16 + dexamethasone-based group ($P = 0.046$) (Table 5).

After treatment for HLH, 35 patients received chemotherapy for lymphoma—CHOP or CHOP-like regimen, 23 patients; GDP regimen, four patients; hyper-CVAD regimen, two patients; DEP regimen, four patients; P-GEMOX regimen, one patient; and SMILE regimen, one patient. Ten (71.4%) patients in the L-DEP/DEP regimen group received chemotherapy for lymphoma, while 15 (71.4%) patients in the VP-16 + dexamethasone-based group received chemotherapy for lymphoma ($P = 1.000$). Four (28.6%) patients in the L-DEP/DEP regimen group received allogeneic hematopoietic stem cell therapy (allo-HSCT), while three (14.3%) patients in the VP-16 + dexamethasone-based group received HSCT (one case of allo-HSCT and two cases of autologous HSCT [auto-HSCT]; $P = 0.401$).

Among the 36 patients in the non-HLH-NK/TCL group, 31 patients received the CHOP regimen combined with pegaspargase, two patients received the GDP regimen combined with pegaspargase, one patient received the P-GEMOX regimen, one patient received the SMILE regimen, and one patient did not receive chemotherapy. Twenty-one patients achieved CR after chemotherapy, while 15 patients achieved PR after chemotherapy. Eighteen patients received radiotherapy after chemotherapy. One patient received auto-HSCT.

By the time of follow-up, the median follow-up time was 125 days (range, 2 to 2408). Among the 36 patients in the non-HLH-NK/TCL group, six patients were lost to follow-up. The 2-year OS rate of the remaining 30 patients was 53.3%, while the 5-year survival rate was 13.3%. The median overall survival was 498 days. The causes of death for patients in the non-HLH-NK/TCL group were progression of lymphoma. Among the 48 patients with NK/T-LAHLH, only six patients were alive at the last follow-up. Nine patients were lost to follow-up. Among them, two received allo-HSCT and two received auto-HSCT. The other two patients received standard chemotherapy of L-GDP and L-ECHOP after HLH treatment. The median overall survival was 65 days. Among NK/T-LAHLH, 35 cases died of the progression of HLH, and four cases died of severe infection complications. A significant intergroup difference in OS was noted ($P < 0.01$) (Fig. 1). Among NK/T-LAHLH, the median survival time was 124 days in the L-DEP/DEP group and 58 days in the VP-16 + dexamethasone-based group ($P = 0.088$) (Fig. 2).

Discussion

LAHLH is a common secondary HLH with a very poor prognosis. NK/T-cell lymphoma cases accounts for the highest proportion (35%) of tumor-associated HLH cases [4]. The incidence of HLH in NK/T-cell lymphoma is currently unknown. Jia et al. reviewed 202 cases of extranodal NK/T-cell lymphoma, of which 11.4% (23/202) cases developed HLH [11]. Li et al. reported that 7.1% (21/295) patients diagnosed with nasal type extranodal NK/T-cell lymphoma also developed HLH [12]. However, in our study, the incidence of HLH in NK/T-cell lymphoma was as high as 57.1% (48/84 patients). The main reason for this high incidence is that our center has been focusing on HLH diagnosis and treatment. However, in a study of 20 patients with NK/mature T-LAHLH, 70% (14/20) patients had NK/T-LAHLH [7]. Because HLH is a very rare disease, the reported studies had a small sample size; hence, its exact incidence is unclear.

To understand the characteristics of NK/T-LAHLH, we compared the clinical and laboratory characteristics

Table 3 Baseline characteristics of patients in L-DEP/DEP regimen and VP-16 + dexamethasone-based regimens

	L-DEP/DEP regimen Number ($n = 14$)/percentage (%)	VP-16 + dexamethasone regimen Number ($n = 21$)/percentage (%)	*P* value
Gender			1.000
Male	10/71.4	15/71.4	
Female	4/28.6	6/28.6	
Age (years) mean ± SE	34.36 ± 4.52	30.05 ± 4.52	0.954
Stage			1.000
I–II	1/7.1	2/9.5	
III–IV	13/92.9	19/90.5	
B symptoms	14/100.0	21/100.0	
IPI			
0–1	1/7.1	0/0	0.400
2–3	11/78.6	14/66.7	0.704
4–5	2/14.3	7/33.3	0.262
Fever (≥ 38.5 ℃)	14/100.0	21/100.0	
Splenomegaly	12/85.7	12/57.1	0.137
Cytopenia for at least two cell lines	8/57.1	13/61.9	1.000
LDH > 240 U/L (%)	14/100.0	17/81.0	0.133
BM involvement (%)	4/28.6%	11/52.4	0.296
HLH onset			1.000
At lymphoma diagnosis	12/85.7	17/81.0	
At lymphoma progress	2/14.3	4/19.0	

IPI, International Prognostic Index; *LDH*, lactate dehydrogenase; *HLH*, hemophagocytic lymphohistiocytosis

of NK/T-cell lymphoma patients with HLH with those of patients without HLH. We found that patients with HLH generally have poor clinical and laboratory indicators. These findings are consistent with those reported in previous studies [11–13]. For example, Jia et al. compared the clinical and laboratory characteristics of NK/T-LAHLH patients with those of patients with non-HLH-NK/TCL [11]. They found that bone marrow involvement and decreased serum albumin levels were independent risk factors for patients with extranodal NK/T-cell lymphoma developing HLH. Li et al. reported that bone marrow involvement, hepatosplenomegaly, and elevated LDH levels were risk factors for NK/T-LAHLH [12]. The above clinical and laboratory characteristics suggest that affected patients are seriously ill and have a poor prognosis. Active and effective treatments are urgently needed to control disease progression. After multivariate analysis, we found that elevated lactate dehydrogenase and Ann Arbor stage III/IV were high risk factors for HLH in patients with NK/T-cell lymphoma.

There is currently no standard effective treatment for NK/T-LAHLH. It is unclear whether the treatment for LAHLH treats HLH or lymphoma first or the combination of the two treatments can produce better results. For the treatment of LAHLH, the HLH-94/04 protocol is the main treatment. In our study, 21 patients received VP-16 + dexamethasone-based regimens; of them, nine (42.9%) patients achieved PR. Chemotherapy with corticosteroids combined with immunosuppressive or cytotoxic drugs has also been reported to be effective for the treatment of LAHLH [14, 15]. Other treatment options include the DEP (combination with or without pegaspargase) regimen. In our study, 14 patients received L-DEP/DEP; of them, 11 (78.6%) patients achieved PR. The 2-week ORR of patients in the L-DEP/DEP regimen group was higher than that of patients in the VP-16 + dexamethasone-based group ($P = 0.046$).

We believe that liposomal doxorubicin is one of the reasons for this. After the doxorubicin liposome enters the human body, it is primarily engulfed by monocytes and macrophages in the reticuloendothelial system. This is important for controlling HLH. Another important reason for this is the application of pegaspargase. During the last decade, some pegaspargase- or L-asparaginase-based regimens have been used to treat extranodal NK/T-cell lymphoma patients with or without HLH. Han et al. reported the addition of pegaspargase to the NK/T-LAHLH regimen resulted in encouraging outcomes [16]. In the study by Li et al., seven patients with NK/T-LAHLH who were treated with the pegaspargase-based MEDA regimen (methotrexate, etoposide, dexamethasone, and pegaspargase) had an ORR of 85.4% [17].

Table 4 Comparison of laboratory data of patients with HLH in L-DEP/DEP and VP-16 + dexamethasone-based groups

Laboratory data	L-DEP/DEP	VP-16 + dexamethasone-based	*P* value
WBC ($\times 10^9$/L), mean ± SE ($3.5–9.5 \times 10^9$/L)	2.94 ± 0.45	1.90 ± 0.24	0.036
Hb (g/L), mean ± SE (130–175 g/L)	102.36 ± 5.25	92.05 ± 4.13	0.128
PLT ($\times 10^9$/L), mean ± SE ($125–350 \times 10^9$/L)	60.15 ± 8.35	57.71 ± 13.76	0.897
Ferritin (μg/L), mean ± SE (11.00–306.00 μg/L)	5214.47 ± 1371.41	8148.55 ± 2797.02	0.414
ALB (g/L), mean ± SE (40–55 g/L)	28.85 ± 1.89	31.08 ± 1.28	0.326
ALT (U/L), mean ± SE (7.0–44.0 U/L)	133.57 ± 33.89	138.26 ± 28.80	0.917
AST (U/L), mean ± SE (13.0–35.0 U/L)	155.46 ± 30.10	157.43 ± 30.91	0.965
TBIL (μmol/L), median (range) (3.42–17.10 μmol/L)	38.28 (10.67–230.80)	29.72 (8.90–373.00)	0.851
LDH (U/L), mean ± SE (120–250 U/L)	848.86 ± 127.01	786.89 ± 107.56	0.711
Fbg (g/L), mean ± SE (2–4 g/L)	1.65 ± 0.24	1.37 ± 0.17	0.326
TG (mmol/L), median (range) (0.57–1.70 mmol/L)	2.24 (1.37–10.02)	3.00 (0.98–5.96)	0.159
Soluble CD25 (pg/mL), mean ± SE (< 6400 pg/mL)	29,410.27 ± 3691.48	29,435.26 ± 3831.18	0.996
PBMC EBVDNA (copy/mL) median (range)	89,000 (2000–820,000)	524,000 (220–70,000,000)	0.016
Plasma EBVDNA (copy/mL) median (range)	95,000 (3300–5,500,000)	100,000 (3800–1,600,000)	0.782

HLH, hemophagocytic lymphohistiocytosis; *WBC*, white blood cells; *Hb*, hemoglobin; *PLT*, platelets; *ALB*, albumin; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *TBIL*, total bilirubin; *LDH*, lactate dehydrogenase; *Fbg*, fibrinogen; T*G*, Triglyceride; BM, bone marrow

Table 5 Response of HLH and treatment for lymphoma in L-DEP/DEP and VP-16 + dexamethasone-based groups

	L-DEP/DEP	VP-16 + dexamethasone-based	*P* value
	N = 14	*N* = 21	
Response of HLH			
CR of 2 weeks	0	0	
PR of 2 weeks	11 (78.6%)	9 (42.6%)	0.046
ORR of 2 weeks	11 (78.6%)	9 (42.6%)	0.046
Chemotherapy for lymphoma	10 (71.4%)	15 (71.4%)	1.000
HSCT	4 (28.6%)	3 (14.3%)	0.401
allo-HSCT	4 (28.6%)	1 (4.76%)	0.071
auto-HSCT	0	2 (9.52%)	0.353

CR, complete response; *PR*, partial response; *ORR*, overall response rate

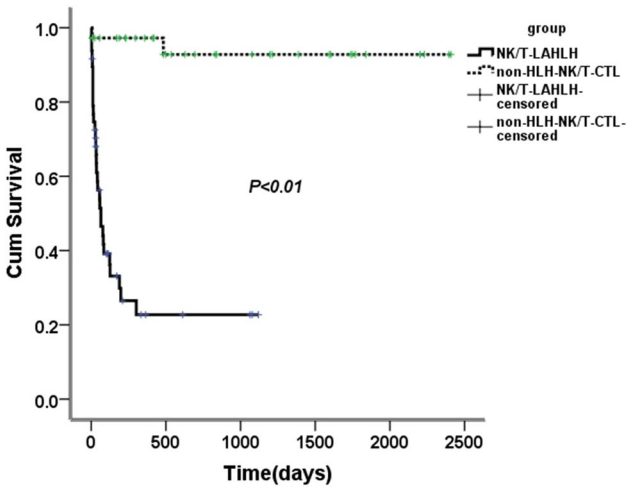

Fig. 1 Significant intergroup difference in overall survival

Pegaspargase has been reported to have a positive therapeutic effect on EBV-HLH. For example, Wang et al. reported that refractory EBV-HLH patients were treated with the L-DEP regimen, with an ORR of 85.7%, and that the median EBV DNA level decreased significantly after treatment [18]. It may be possible that pegaspargase targets EBV-infected T-cells and NK cells since they may not be able to synthesize L-asparagine [19]. After entering cells, pegaspargase can induce the hydrolysis of L-asparagine and prevent T-cells and NK cells from synthesizing the

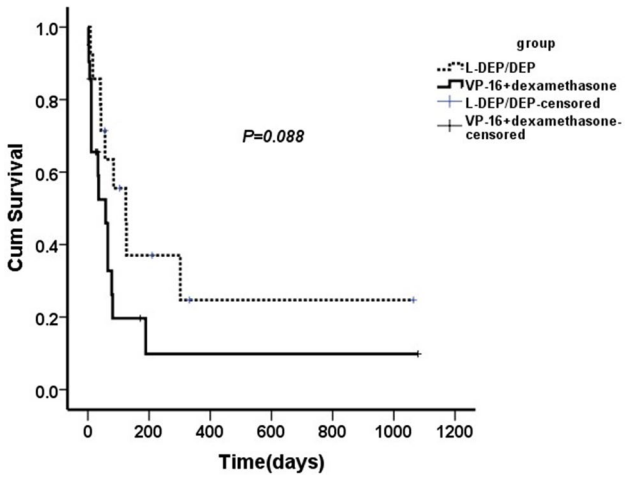

Fig. 2 The median survival time in the L-DEP/DEP group and in the VP-16 + dexamethasone-based group among NK/T-LAHLH

corresponding necessary proteins, ultimately inhibiting cellular proliferation and resulting in a decline in EBV-DNA. In addition, PBMC EBV DNA copies in the VP-16 + dexamethasone-based group were higher than those in the L-DEP/DEP group, which may be another reason for the better treatment effect in the DEP group. NK/T-cell lymphoma is EBV-associated lymphoma.

Both EBV and lymphoma participate in the occurrence and progression of HLH in patients with NK/T-cell lymphoma. Some studies have reported that high-load EBV-DNA triggers EBV-related HLH and is associated with poor prognosis [8, 18]. For example, a study by Wang et al. found that EBV-HLH patients with EBV-DNA $< 1 \times 10^5$ copies/mL had a longer survival time than those with EBV-DNA $> 1 \times 10^5$ copies/mL and that patients with EBV-DNA $< 1 \times 10^6$ copies/mL had a longer survival time than those with EBV-DNA $> 1 \times 10^6$ copies/mL [18]. Li et al. found that a low plasma EBV-DNA level was a prognostic factor for better survival [17]. Further, there are also reports of multidrug combination chemotherapy options such as CHOP or CHOP-like regimens for the treatment of LAHLH. However, in our study, eight patients received CHOP or CHOP-like chemotherapy regimens directly; only two (33.3%) of the six patients available for evaluation achieved PR.

HSCT is another important factor that affects the prognosis of patients with NK/T-LAHLH. It is unknown whether HSCT can benefit patients with NK/T-LAHLH in terms of survival. In Yu et al.'s study, two patients with T-LAHLH who received allo-HSCT had a favorable prognosis [20]. In Machaczka et al.'s study, one patient with T-LAHLH achieved long-term survival after allo-HSCT [21]. In our study, there was no difference between the L-DEP/DEP group and the VP-16 + dexamethasone-based group receiving HSCT. The median survival time of NK/T-LAHLH patients in the L-DEP/DEP regimen group was 124 days, which was longer than that of patients in the VP-16 + dexamethasone-based group (58 days); however, the difference was not statistically significant ($P = 0.088$). This may be related to the small sample size. Therefore, studies with a large sample size are needed to confirm whether the L-DEP/DEP regimen can improve the prognosis of patients with NK/T-LAHLH.

Conclusions

In conclusion, patients with NK/T-LAHLH had poorer survival than those without HLH. For NK/T-LAHLH patients, the L-DEP/DEP regimen may have a better 2-week response rate than VP-16 + dexamethasone-based regimens. However, prospective multicenter clinical trials are needed to explore the importance of the L-DEP/DEP regimen in the early treatment of NK/T-LAHLH.

Funding This work was supported by the National Natural Science Foundation of China (No. 81871633).

Declarations

Ethical approval The work was approved by the Institutional Review Board of Friendship Hospital. The study has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all participants included in this study.

Conflict of interest The authors declare no competing interests.

References

1. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G (2007) HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 48(2):124–131
2. Skinner J, Yankey B, Shelton BK (2019) Hemophagocytic lymphohistiocytosis. AACN Adv. Crit Care 30(2):151–164
3. Rivière S, Galicier L, Coppo P, Marzac C, Aumont C, Lambotte O, Fardet L (2014) Reactive hemophagocytic syndrome in adults: a retrospective analysis of 162 patients. Am J Med 127(11):1118–1125
4. Lehmberg K, Nichols KE, Henter JI, Girschikofsky M, Greenwood T, Jordan M, Kumar A, Minkov M, La Rosée P, Weitzman S, Study Group on HemophagocyticLymphohistiocytosis Subtypes of the Histiocyte Society (2015) Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. Haematologica 100(8):997–1004

5. Fugl A, Andersen CL (2019) Epstein-Barr virus and its association with disease - a review of relevance to general practice. BMC Fam Pract 20(1):62
6. Goudarzipour K, Kajiyazdi M, Mahdaviyani A (2013) Epstein-Barr virus-induced hemophagocytic lymphohistiocytosis. Int J Hematol Oncol Stem Cell Res 7(1):42–45
7. Takahashi N, Miura I, Chubachi A, Miura AB, Nakamura S (2001) A clinicopathological study of 20 patients with T/natural killer (NK)-cell lymphoma-associated hemophagocytic syndrome with special reference to nasal and nasal-type NK/T-cell lymphoma. Int J Hematol 74(3):303–308
8. Ishii E, Ohga S, Imashuku S, Yasukawa M, Tsuda H, Miura I, Yamamoto K, Horiuchi H, Takada K, Ohshima K, Nakamura S, Kinukawa N, Oshimi K, Kawa K (2007) Nationwide survey of hemophagocytic lymphohistiocytosis in Japan. Int J Hematol 86(1):58–65
9. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V (2007) International Harmonization Project on Lymphoma Revised response criteria for malignant lymphoma. J Clin Oncol 25(5):579–86
10. Marsh RA, Allen CE, McClain KL, Weinstein JL, Kanter J, Skiles J, Lee ND, Khan SP, Lawrence J, Mo JQ, Bleesing JJ, Filipovich AH, Jordan MB (2013) Salvage therapy of refractory hemophagocytic lymphohistiocytosis with alemtuzumab. Pediatr Blood Cancer 60(1):101–9
11. Jia J, Song Y, Lin N, Liu W, Ping L, Zheng W, Wang X, Xie Y, Tu M, Zhang C, Ying Z, Deng L, Ding N, Zhu J (2016) Clinical features and survival of extranodal natural killer/T cell lymphoma with and without hemophagocytic syndrome. Ann Hematol 95(12):2023–2031
12. Li N, Zhang L, Liu J, Zhang J, Weng HW, Zhuo HY, Zou LQ (2017) A clinical study of 21 patients with hemophagocytic syndrome in 295 cases diagnosed with nasal type, extranodal nature killer/T cell lymphoma. Cancer Biol Ther 18(4):252–256. https://doi.org/10.1080/15384047.2017.1295176
13. Liu YZ, Bi LQ, Chang GL, Guo Y, Sun S (2019) Clinical characteristics of extranodal NK/T-cell lymphoma-associated hemophagocytic lymphohistiocytosis. Cancer Manag Res 23(11):997–1002
14. Han L, Zhang M, Li L, Zhang L, Wu J, Li X, Wang X, Young KH, Fu X, Ma W, Sun Z, Zhang X, Chang Y, Qiao Z (2014) Natural killer/T-cell lymphoma-associated hemophagocytic syndrome: a case report. Oncol Lett 8(2):886–890
15. Wei L, Yang L, Cong J, Ye J, Li X, Yao N, Yang J, Ding J, Wang J (2020) Using etoposide + dexamethasone-based regimens to treat nasal type extranodal natural killer/T-cell lymphoma-associated hemophagocytic lymphohistiocytosis. J Cancer Res Clin Oncol 6:1–7
16. Han L, Li L, Wu J, Li X, Zhang L, Wang X, Fu X, Ma W, Sun Z, Zhang X, Chang Y, Guo S, Zhang M (2014) Clinical features and treatment of natural killer/T cell lymphoma associated with hemophagocytic syndrome: comparison with other T cell lymphoma associated with hemophagocytic syndrome. Leuk Lymphoma 55(9):2048–2055
17. Li DH, Zhang XY, Du C, Zhang WH, Chang J, Ma YJ, Li ZC, Hao SG, Ding H, Tao R (2017) Successful treatment of extranodal natural killer/T-cell lymphoma-associated hemophagocytic lymphohistiocytosis with MEDA chemotherapy. Leuk Lymphoma 58(5):1238–1241
18 Wang J, Wang Y, Wu L, Zhang J, Lai W, Wang Z (2016) PEG-aspargase and DEP regimen combination therapy for refractory Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. J Hematol Oncol 9(1):84
19. Ando M, Sugimoto K, Kitoh T, Sasaki M, Mukai K, Ando J, Egashira M, Schuster SM, Oshimi K (2005) Selective apoptosis of natural killer-cell tumours by l-asparaginase. Br J Haematol 130(6):860–868
20. Yu JT, Wang CY, Yang Y, Wang RC, Chang KH, Hwang WL, Teng CL (2013) Lymphoma-associated hemophagocytic lymphohistiocytosis: experience in adults from a single institution. Ann Hematol 92(11):1529–1536
21. Machaczka M, Nahi H, Karbach H, Klimkowska M, Hägglund H (2012) Successful treatment of recurrent malignancy-associated hemophagocytic lymphohistiocytosis with a modified HLH-94 immunochemotherapy and allogeneic stem cell transplantation. Med Oncol 29(2):1231–1236