Dose-adjusted EPOCH regimen as first-line treatment for non-Hodgkin lymphoma-associated hemophagocytic lymphohistiocytosis: a single-arm, open-label, phase II trial

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder characterized by uncontrolled T/natural killer (NK) cells and macrophage activation and an excessive production of inflammatory cytokines. HLH can be divided into primary (genetic) and secondary (reactive) which is secondary to infection, autoimmune disease, malignant tumors, and other causes.[1-4] Lymphoma accounted for 67% in adult patients with HLH in the context of malignant tumors.[2] First-line treatments of lymphoma-associated HLH (LA-HLH) have not been prospectively studied until now. No clear conclusions have been drawn as to whether an HLH-directed, lymphoma-directed, or combined approach should initially be adopted. Therefore, we aimed to assess the efficacy, safety, and feasibility of the DA-EPOCH±R regimen[5,6] which contains the drugs both for HLH and non-Hodgkin lymphoma (NHL) as a first-line treatment for NHL-associated HLH.

We did a single-arm, open-label, phase II clinical trial in previously untreated patients diagnosed as NHL with HLH (*clinicaltrials.gov identifier: 01818908*). The eligibility and exclusion criteria are summarized in *Online Supplementary Table S1*. The study protocol is available online. B-cell NHL (B-NHL) patients with HLH were programmed to receive six cycles of DA-EPOCH-R regimen while T/NK-NHL patients with HLH were programmed to receive six cycles of DA-EPOCH regimen. Also, after achieving ≥ partial response (PR) after six cycles of DA-EPOCH±R regimen, autologous stem cell transplantation (ASCT) for B-NHL or allogeneic stem cell transplantation (allo-SCT) for T/NK-NHL was followed as consolidation therapies. Details of the DA-EPOCH regimen have been published elsewhere.[5,6] Courses were repeated every three weeks. Central nervous system (CNS) prophylaxis was considered with 4-8 doses of intrathecal methotrexate (15 mg), cytarabine (50 mg) and dexamethasone (5 mg) for all patients.

Patients' responses were assessed by investigator according to standard Cheson criteria[7] or Deauville criteria [Deauville score 1-3 considered positron emission tomography (PET) negative] for PET/computed tomography (CT)[8] after three cycles, at the end of treatment and/or after the ASCT/allo-SCT. Follow-up assessments were planned every three months for one year, every six months for two more years, and yearly thereafter, including physical examination, laboratory tests, and enhanced CT scans. The primary end point was the overall response rate (ORR). The secondary outcome measures were progression-free survival (PFS), overall survival (OS), and the number of participants with adverse events. PFS and OS were calculated up to the last follow-up date (November 1st, 2018) of this report. Safety was defined as the incidence and severity of adverse events according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Fisher exact test was applied to categorical variables and the Mann-Whitney U test to continuous variables. Survival curves were constructed by the

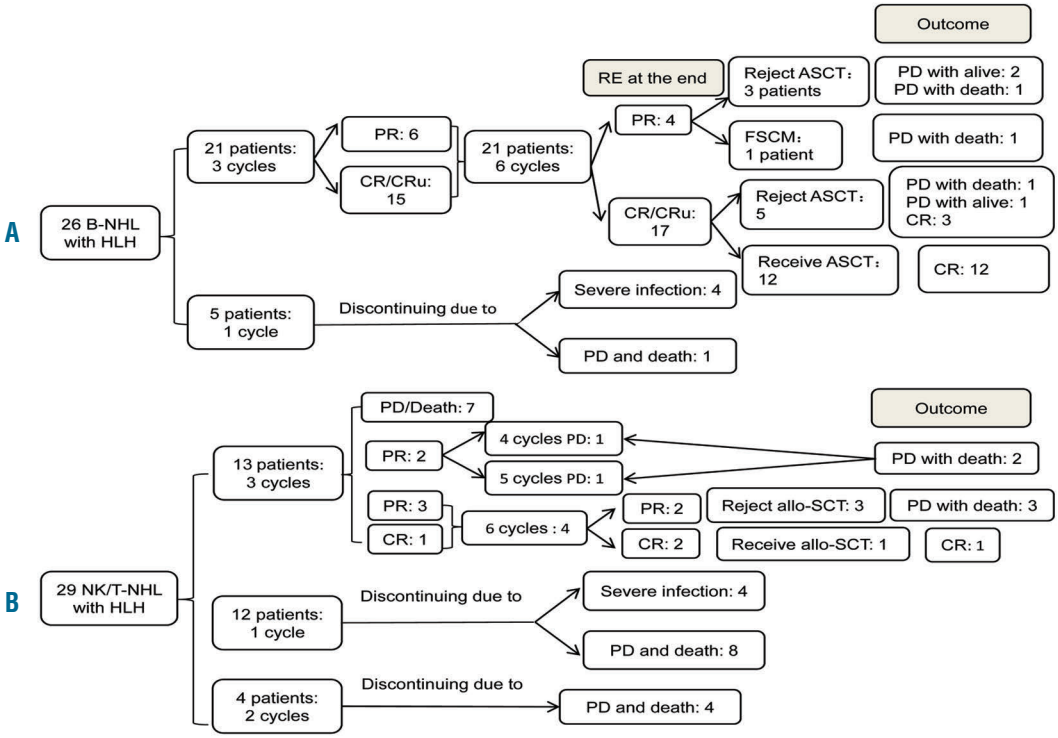

Figure 1. Treatment responses and outcomes for non-Hodgkin lymphoma (NHL) patients with hemophagocytic lymphohistiocytosis (HLH) who were treated with DA-EPOCH±R (A) for 26 B-NHL and (B) for 29 natural killer (NK)/T-NHL patients. allo-SCT: allogeneic stem cell transplantation; ASCT: autologous stem cell transplantation; CR/CRu: complete response/completed response unconfirmed; FSCM: failed to stem cell mobilization; HLH: hemophagocytic lymphohistiocytosis; PR: partial response; PD: progressive disease; RE: response evaluation.

Table 1. Baseline characteristics of patients.

	B-NHL (N=26)	T/NK-NHL (N=29)	P
Men	15 (57.7%)	15 (51.7%)	0.657
Median age (range)	53 (21–69)	43 (17–71)	0.002
Stage IV	26 (100%)	29 (100%)	1.000
Bone marrow involvement	26 (100%)	29 (100%)	1.000
≥2 extranodal sites	15 (57.6%)	15 (51.7%)	0.657
B symptoms	26 (100%)	29 (100%)	1.000
ECOG performance status score≥2	18 (69.2%)	29 (100%)	0.001
Lactate dehydrogenase >ULN	22 (84.6%)	26 (89.7%)	0.576
Serum albumin>35 g/L	14 (53.8%)	28 (96.5%)	<0.001
EBV-DNA level>5000 copies/mL	13 (50.0%)	25 (86.2%)	0.004
HBV status (HBsAg positive)	3 (11.5%)	3 (10.3%)	0.887
HCV status	0	0	1.000
HIV status	0	0	1.000
Elevated AST/ALT levels	9 (34.6%)	23 (79.3%)	<0.001
IPI score			
0-1	0	0	
2	5 (19.2%)	0	
3	9 (34.6%)	12 (41.4%)	
4	9 (34.6%)	15 (51.7%)	
5	3 (11.5%)	2 (6.9%)	
HLH diagnosis:			
1 Fever	25 (96.1%)	29 (100%)	0.287
2 Hepatosplenomegaly	20 (76.9%)	23 (79.3%)	0.831
3 Cytopenias affecting ≥ 2 of 3 lineages in peripheral blood	26 (100%)	29 (100%)	1.000
4 Hypertriglyceridemia and/or hypofibrinogenemia	20 (76.9%)	26 (89.7%)	0.202
5 Hemophagocytosis in bone marrow or spleen or lymph nodal	23 (88.4%)	29 (100%)	0.060
6 Low or absent NK-cell activity	ND	ND	-
7 Serum-ferritin ≥ 500 ug/L	26 (100%)	29 (100%)	1.000
8 Soluble CD25 (sIL-2 receptor)	11 (42.3%)	21 (72.4%)	0.024

EBV: Epstein-Barr virus; ALT/AST: alanine transaminase/aspartate aminotransferase; HBV: hepatitis B virus; HCV: hepatitis C virus; HLH: hemophagocytic lymphohistiocytosis; HIV: human immunodeficiency virus; IPI: International Prognostic Index; NK: natural killer; ND: not done; NHL: non-Hodgkin lymphoma.

Kaplan-Meier method, and the log-rank test used to test for significant differences. Statistical analyses were performed using SPSS software for Windows v.17.0 (SPSS Inc., Chicago, IL, USA). $P<0.05$ was considered significant.

Between March 27th 2013 and December 21st 2015, 62 patients were assessed for eligibility, and 55 patients (88.7%) were enrolled to receive treatment and included in the intention-to-treat analysis (*Online Supplementary Figure S1*). For the 26 B-NHL patients with HLH, eight (30.7%) patients who were diagnosed based on lymph node biopsy were all the subtype of diffuse large B-cell lymphoma (DLBCL) [7 patients were the subtype of DLBCL, not otherwise specified (NOS) and the other one was the subtype of T-cell-/histiocyte-rich large B-cell lymphoma]. The other 18 (69.2%) patients with no special subtypes were diagnosed based on morphology, flow cytometric immunophenotyping, IgH rearrangement of bone marrow and immunohistochemistry of bone marrow biopsy. For the 29 T/NK-NHL patients with HLH, two (6.9%) patients were diagnosed as angioimmunoblastic T-cell lymphoma (AITL), two (6.9%) patients were anaplastic large cell lymphoma (ALCL), ALK negative, seven (24.1%) patients were extra-nodal NK/T-cell lymphoma (ENKTL), nasal type, two (6.9%) patients were aggressive NK cell leukemia (ANKL), three (10.3%) patients were peripheral T-cell lymphoma (PTCL), NOS, the other 13 (44.8%) patients with no special subtypes were T/NK-NHL were diagnosed based on morphology, flow cytometric immunophenotyping [including T-cell receptor (TCR) VB frequency analysis and KIR expression profile], TCR rearrangement of bone marrow and immunohistochemistry of bone marrow biopsy. Patients' other baseline characteristics are summarized in Table 1.

Considering all B-NHL patients, a median of six cycles of DA-EPOCH-R (range 1-6) were given. ORR at the end of six cycles of DA-EPOCH-R regimen was 80.7% (21 of 26). For these 21 patients who achieved ≥PR after six cycles of DA-EPOCH-R regimen, only 12 patients (57.1%) received ASCT while eight patients rejected ASCT for personal reasons and one patient failed stem cell mobilization (FSCM) (details in Figure 1A). At a median follow up of 52 months (35-75 months) for B-NHL patients with HLH, 5-year PFS was 56.7±9.9% and 5-year OS was 73.1±8.7% (Figure 2A). Exploratory outcomes, assessed by univariate analyses, suggested that International Prognostic Index (IPI) score of 4-5 and

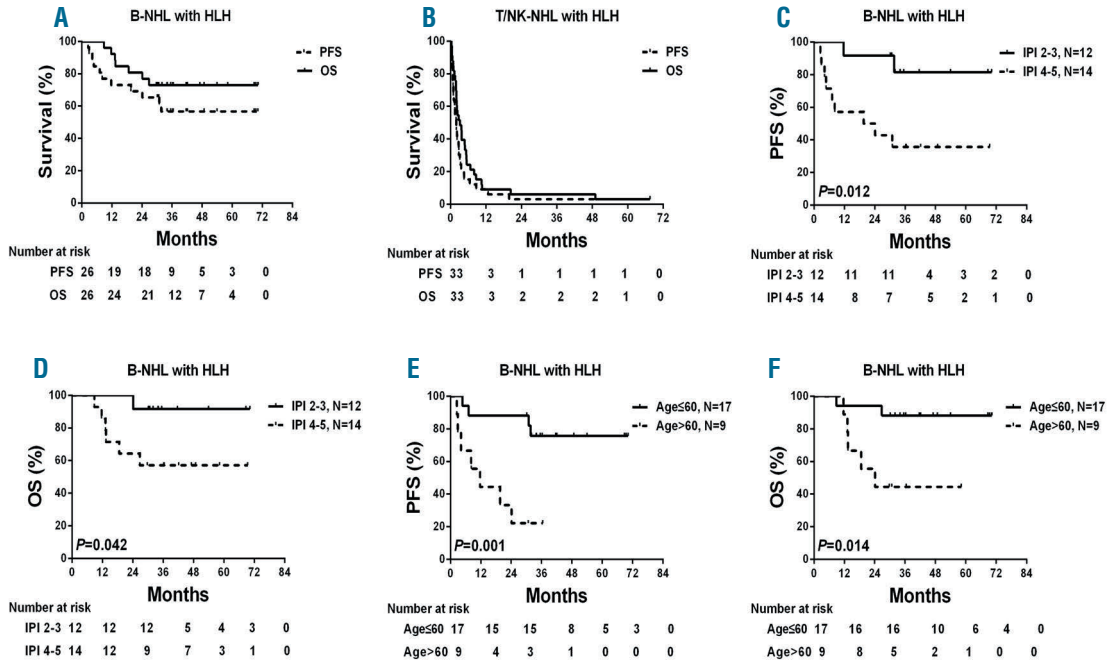

Figure 2. Survival analysis. Progression-free survival (PFS) and overall survival (OS) for B-NHL (A) and T/natural killer non-Hodgkin lymphoma (NK-NHL) (B) patients treated with DA-EPOCH; PFS and OS for B-NHL patients for different risk factors: (C) and (D) for IPI risk factor, (E) and (F) for age risk factor.

age >60 years were predictive of shorter PFS (P=0.012 and P=0.001) and OS (P=0.042 and P=0.014) (Figure 2C-F). For the 12 patients receiving ASCT, all patients were alive with CR (5-year PFS and OS were 100%), while for the eight patients who did not receive ASCT, 5-year PFS and OS were only 29.6±16.4% and 66.7±15.7% (*Online Supplementary Figure S2*).

For all T/NK-NHL patients, a median of two cycles of DA-EPOCH-R were administered (range 1-6). ORR at the end of six cycles of DA-EPOCH-R regimen was 13.8% (4 of 29). At the follow-up deadline, only one patient who achieved CR after six cycles of treatment and following allo-SCT was alive while the other patients had all died (see Figure 1B for details). Due to the fact that nearly all NK/T-NHL patients with HLH had died within one year, 3-month PFS and OS rate was 24.1±7.9% and 55.2±9.2%, 6-month PFS and OS rates were 10.3±5.7% and 24.1±7.9% and 12-month PFS and OS rates were 3.4±3.4% and 3.4±3.4% (Figure 2B). None of the risk factors were of predictive value for PFS and OS because most of the patients experienced disease progression within three months.

The percent of each dose level administered over treatment cycles for all patients are described in *Online Supplementary Table S2*. Grade 3/4 thrombocytopenia occurred on 14.6% (30 of 205) of cycles. Grade 3/4 neutropenia toxicities occurred on 43.9% (90 of 205) of cycles. No cardiac complications occurred.

Currently, HLH-94 or HLH-04 regimens remain the standard HLH treatment strategies.[9] However, no effective responses were observed for LA-HLH.[10] Etoposide and corticosteroids that have a multi-immunosuppression effect are the core drugs in HLH-04 regimen. However, for LA-HLH, these drugs are not enough to treat the lymphoma. As we know, CHOP regimen which included cyclophosphamide, doxorubicin, vincristine, and prednisone was the basis of cytotoxic chemotherapy for lymphomas, especially for B-NHL. Therefore, based on our experience in the treatment of LA-HLH, we chose the DA-EPOCH regimen,[5,6] which contains the drugs both for HLH and lymphoma as induction strategy for LA-HLH.

In the present study, ORR of the 26 B-NHL patients with HLH was 80.7% (21 of 26) which is higher than the result reported by Yu *et al.*[11] For the 21 B-NHL patients who completed six cycles of treatment, all patients responded to the regime of DA-EPOCH-R; this is similar to results in 71 DLBCL patients without HLH treated with DA-EPOCH-R as first-line treatment reported by Wilson et al. (ORR: 98%).6 Furthermore, 5-year PFS and OS were 56.7±9.9% and 73.1±8.7% for these B-NHL patients with HLH, which were much higher than previous reports.[11,12]

So far, there have been few studies that focus on the role of ASCT in LA-HLH. Data from Shimazaki *et al.*[12] demonstrated that high-dose chemotherapy followed by ASCT can improve survival for B-NHL patients with HLH. In our study, patients who received ASCT (5-year PFS and OS were 100%) had superior outcomes than those who did not receive ASCT. Among the five patients with CR status after six cycles of DA-EPOCH-R who rejected receiving ASCT, two patients had disease-progression while so far the other three have all maintained CR status. Given the small sample size and selection bias, it is still unclear as to the additional benefits of ASCT in patients who achieve CR post DA-EPOCH-R.

Many previous studies have demonstrated that NK/T-NHL had a worse prognosis than B-NHL and had a high mortality rate in LA-HLH.[11,13-15] Even with better supportive care for all the patients, also in our study,12-month OS rate was only 3.4±3.4%. Therefore, enhanced aggressive regimen of DA-EPOCH cannot improve outcomes

for NK/T-NHL patients with HLH.[2] In our study, only one patient who received allo-SCT was alive with CR after 5-year follow up. Therefore, there is a particular need for future investigation of timely and effective treatment for T/NK-NHL patients with HLH.

In summary, DA-EPOCH-R regimen as front-line treatment followed by ASCT as consolidation treatment demonstrates a high efficacy and safety for B-NHL patients with HLH. However, DA-EPOCH cannot improve outcomes for T/NK-NHL patients with HLH. Allo-SCT is currently the only effective way to prolong survival of NK/T-NHL patients with HLH. Therefore, novel target agents and treatment protocols are urgently needed to improve outcomes for T/NK-NHL patients with HLH.

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References

1. Henter JI, Aricò M, Egeler RM, et al. HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis. HLH study Group of the Histiocyte Society. Med Pediatr Oncol. 1997;28(5):342-347.
2. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, et al. Adult haeophagocytic syndrome. Lancet. 2014;383(9927):1503-1516.
3. Parikh SA, Kapoor P, Letendre L, et al. Prognostic factors and outcomes of adults with hemophagocytic lymphohistiocytosis. Mayo Clin Proc. 2014;89(4):484-492.
4. Rivière S, Galicier L, Coppo P, et al. Reactive hemophagocytic syndrome in adults: a retrospective analysis of 162 patients. Am J Med. 2014;127(11):1118-1125.
5. Wilson WH, Grossbard ML, Pittaluga S, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: A pharmacodynamic approach with high efficacy. Blood. 2002;99(8):2685-2693.
6. Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-Cell lymphoma with analysis of germinal center and post-germinal center biomarkers. J Clin Oncol. 2008;26(16):2717-2724.
7. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-586.
8. Meignan M, Gallamini A, Haioun C, et al. Report on the 5th International Workshop on Positron Emission Tomography in Lymphoma held in Menton, France, 19-20 September 2014. Leuk Lymphoma. 2015;56(5):1229-1232.
9. Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124-131.
10. Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. Am J Hematol. 2015;90(3):220-224.
11. Yu JT, Wang CY, Yang Y, Wang RC, Chang KH, Hwang WL, Teng CL. Lymphoma-associated hemophagocytic lymphohistiocytosis: experience in adults from a single institution. Ann Hematol. 2013;92(11):1529-1536.
12. Shimazaki C, Inaba T, Nakagawa M. B-cell lymphoma-associated hemophagocytic syndrome. Leuk Lymphoma. 2000;38(1-2):121-130.
13. Ishii E, Ohga S, Imashuku S, et al. Nationwide survey of hemophagocytic lymphohistiocytosis in Japan. Int J Hematol. 2007;86(1):58-65.
14. Sano H, Kobayashi R, Tanaka J, et al. Risk factor analysis of non-Hodgkin lymphoma-associated haemophagocytic syndromes: a multicenter study. Br J Haematol. 2014;165(6):786-792.
15. Bhatt NS, Oshrine B, An Talano J. Hemophagocytic lymphohistiocytosis in adults. Leuk Lymphoma. 2019;60(1):19-28.