Ruxolitinib-based regimen in children with primary hemophagocytic lymphohistiocytosis

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Abstract

Primary hemophagocytic lymphohistiocytosis (pHLH) is a rare immune disorder and hematopoietic stem cell transplantation (HSCT) is the only potentially curative treatment. Given the high pre-HSCT mortality of pHLH patients reported in the HLH-2004 study (17%), more regimens to effectively control the disease and form a bridge with HSCT are needed. We conducted a retrospective study of pHLH children treated by ruxolitinib (RUX)-based regimen. Generally, patients received RUX until HSCT or unacceptable toxic side-effect. Methylprednisolone and etoposide were added sequentially when the disease was suboptimally controlled. The primary end point was 1-year overall survival. Twenty-one pHLH patients (12 previously treated and 9 previously untreated) were included with a median follow-up of 1.4 years. At last follow-up, 17 (81.0%) patients were alive with a 1-year overall survival of 90.5% (95% confidence interval: 84.1-96.9). Within the first 8 weeks, all patients had an objective response, of which 19 (90.5%) achieved complete response (CR) and two (9.5%) achieved partial response (PR) as a best response. Seventeen (81.0%) patients received HSCT, of which 13 (76.5%) had CR, three (17.6%) had PR and one (5.9%) had disease reactivation at the time of HSCT. Fifteen (88.2) patients were alive post-HSCT. Notably, eight (38.1%) patients received zero doses of etoposide, suggesting the potential of RUX-based regimen to reduce chemotherapy intensity. Patients tolerated RUX-based regimen well and the most frequently observed adverse events were hematologic adverse events. Overall, RUX-based regimen was effective and safe and could be used as a bridge to HSCT for pHLH children.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare hematologic disorder characterized by pathologic immune activation and extreme inflammation.[1,2] Primary HLH (pHLH) is a genetic disorder caused by mutation of genes involved in cytotoxicity machinery of natural killer and $CD8^+$ T cells. pHLH can be diagnosed at any age but typically manifests during childhood. If left untreated, uncontrolled inflammation may result in severe organ dysfunction and death.[3,4]

As allogeneic hematopoietic stem cell transplantation (HSCT) is the only possible curative therapy for pHLH, it is critical to rapidly control inflammatory response to allow for early HSCT.[5,6] Over the past 20 years, HLH-1994 and HLH-2004 regimen are widely used as a bridge to transplantation and has significantly improved the survival of patient with pHLH. Despite these advancements, pre-HSCT mortality still remains high (17% according to the HLH-2004 study) due to frequent disease recurrence and toxic effects of chemotherapy.[7,8] In addition, as an integral part of regimen, etoposide may have non-negligible long-term side effects including secondary tumor risk.[9]

These dilemmas make pHLH clinical management challenging and encourage physicians to search for new drugs to treat the disease. With increasing understanding of immunopathology of pHLH, two studies investigated efficacy of targeted therapy agents including alemtuzumab and emapalumab. Encouraging results of the studies demonstrate over 90% of patients treated by alemtuzumab as the first-line treatment survived to HSCT and 65% of patients who received emapalumab had a response.[5,10]

Ruxolitinib (RUX), an oral selective JAK1 and 2 inhibitor, has been considered promising targeted drug for HLH because it can inhibit signaling of key proinflammatory cytokines including interferon-γ (IFN-γ) involved in the disease.[11-13] Our previous studies have demonstrated RUX is effective and safe in children with HLH and RUX monotherapy could control the disease rapidly. However, only four patients with pathogenic gene mutations associated with pHLH were enrolled in the two clinical trials.[14,15] Individual case reports have indicated the benefits of using RUX as a bridge to HSCT for patients with pHLH that escaped etoposide-based regimen.[16,17] In addition, several case studies have showed the efficacy of RUX in treating refractory HLH, as well as its potential as a first-line treatment for secondary HLH.[18-20] However, the specific treatment plans in these studies were not uniform and there is still a lack of robust data on efficacy and safety of RUX in pHLH patients.

In order to improve treatment outcomes of pHLH patients and reduce chemotherapy dose intensity, a RUX-based regimen was used in our center. In this study, we reported the findings of our retrospective study evaluating the efficacy and safety of RUX-based regimen in children with pHLH.

Methods

Study design and patients

We conducted a retrospective study of children with pHLH receiving RUX-based therapy in Beijing Children's Hospital from January 2020 to October 2022. This study was approved by the Ethics Committee of Beijing Children's Hospital and the written informed consent from the patients or their parents was obtained. Inclusion criteria included: i) previously treated and untreated children with a diagnosis of pHLH; ii) had active disease before RUX treatment. Patients were excluded for the following reasons: i) did not cooperate with treatment; ii) data were not available.

Ruxolitinib-based treatment and response assessment

In order to improve the treatment outcomes for patients with pHLH and reduce chemotherapy dosage intensity, RUX-based regimen was used as a bridge to HSCT. Patients received oral RUX phosphate tablets treatment within 48 hours after hospital admission, and the dose was 2.5 mg, 5 mg or 10 mg twice a day depending on the body weight (≤10 kg, ≤20 kg or >20 kg, respectively). Generally, RUX treatment was continued until HSCT unless the occurrence of intolerable adverse events or condition in critically ill (e.g., multiorgan system failure). Additional drugs including methylprednisolone (initially 2 mg/kg/d, tapered off in 8 weeks) and etoposide (100 mg/m^2/dose, once/week, continued until achieving complete response [CR]) were added in order. Methylprednisolone was added during RUX monotherapy if any of the following appeared: HLH relapse, marked worsening or no remission of disease symptoms and HLH-related indicators until day 3, or RUX withdrawal due to intolerance. During RUX plus methylprednisolone treatment, etoposide was added when any of the following appeared: HLH relapse, marked worsening or no remission until day 3 after methylprednisolone was added. One patient with pHLH triggered by Epstein-Barr virus (EBV) infection received low-dose liposomal doxorubicin (25 mg/m^2) and pegaspargase (2,000 U/m^2) as an auxiliary treatment. For patients with central nervous system (CNS) involvement, intrathecal treatment with corticosteroids and methotrexate was performed. When an acceptable donor was available, HSCT would be performed as early as possible. The preconditioning regimen we used was a fludarabine-based myeloablative regimen, including fludarabine, busulfan, cyclophosphamide, etoposide, and rabbit anti-thymocyte globulin.

Treatment response was evaluated twice a week until patients achieved CR. Furthermore, we performed assessments at the designated time points, including on the third day of administering RUX, glucocorticoids, or etoposide, and whenever necessary as determined by the treating physician. The response evaluation criteria are provided in the *Online Supplementary Table S1*, which was mainly based on the criteria previously described with some modifications according to our clinical experience.[21]

Outcomes

The primary outcome of this study was the 1-year overall survival. Secondary outcome included the best response within the first 8 weeks, disease status before HSCT, duration from RUX treatment to HSCT, death before and after HSCT, dose intensity of etoposide chemotherapy, and safety. Overall response (OR) rate included the proportion of patients with a CR and a partial response (PR). Response to treatment was evaluated as previously described, including CR, PR and no response (NR). Adverse events (AE) were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Statistical analysis

Descriptive data are presented as the means ± standard deviation for variables with a normal distribution and the medians (minimum - maximum) for variables without a normal distribution. For categorical variables, number and percentage are presented. Characteristics were compared using two-tailed Student's *t* test or Wilcoxon rank sum test for continuous variables and $\chi 2$ test or Fisher exact test for categorical variables. Kaplan-Meier curves were used to analyze survival, and the log-rank test were used

to compare the differences in survival among patient subgroups. All statistical analyses were conducted using SPSS version 25.0 software (IBM, https://www.ibm.com/analytics/spss-statistics-software) and R version 3.6.3 (R Foundation for Statistical Computing, https://www.r-project.org), and a two-sided *P* value of 0.05 was used to determine the statistical significance.

Results

Patients' characteristics

Between January 2020 and October 2022, a total of 27 children with pHLH were treated with RUX-based regimen at Beijing Children's Hospital and six of them were excluded for various reasons *(Online Supplementary Figure S1)*. Among the 21 patients included in the analysis, nine (42.9%) were previously untreated and 12 (57.1%) were previously treated at other hospitals.

Patient characteristics are summarized in Table 1. The median age was 3.10 years (range, 0.13-15.03 years). Ten (47.6%), six (28.6%), four (19.0%) and one (4.8%) patient had a genetic mutation in *UNC13D*, *PRF1*, *XIAP* and *ITK*, respectively. HLH in seven (33.3%) patients was triggered by EBV infection, and 11 patients (52.4%) had CNS involvement presenting abnormalities in one or more CNS symptoms, cerebrospinal fluid and radiological findings before RUX treatment. Characteristics between previously untreated patients and previously treated patients were consistent.

Among 12 previously treated patients, 12 (100.0%) received glucocorticoids, eight (66.7%) received etoposide, two (16.7%) received cyclosporine A and one (8.3%) received liposomal doxorubicin before RUX treatment. The median duration of previous treatment was 55 days (range, 19-350 days). Seven (58.3%) had a CR and five (41.7%) had a PR as the best response to previous treatment. Before RUX treatment, all the previously treated patients had active

Table 1. Clinical patient characteristics.

Patient subgroup	Total N=21	Previously untreated N=9	Previously treated N=12	*P*
Median age in years (range)	3.10 (0.13-15.03)	3.60 (0.13-7.78)	2.30 (0.15-15.03)	0.098
Sex, N (%) Female Male	 8 (38.1) 13 (61.9)	 4 (44.4) 5 (55.6)	 4 (33.3) 8 (66.7)	 0.604
Gene, N (%) *UNC13D* *PRF1* *XIAP* *ITK*	 10 (47.6) 6 (28.6) 4 (19.0) 1 (4.8)	 4 (44.4) 2 (22.2) 2 (22.2) 1 (11.1)	 6 (50.0) 4 (33.3) 2 (16.7) 0 (0.0)	 0.643
Trigger, N (%) EBV infection Unknown	 7 (33.3) 14 (66.7)	 3 (33.3) 6 (66.7)	 4 (33.3) 8 (66.7)	 1.000
Fever (>38.5°C), N (%)	7 (33.3)	3 (33.3)	4 (33.3)	1.000
Splenomegaly, N (%)	13 (61.9)	6 (66.7)	7 (58.3)	0.697
Neutrophils, $\times10^9$/L (range)	0.81 (0.36-3.40)	0.81 (0.36-3.40)	0.79 (0.51-1.82)	0.808
Platelets, $\times10^9$/L (range)	83 (21-569)	68 (21-152)	85 (55-569)	0.111
Hemoglobin, g/L (range)	83 (62-127)	83 (69-105)	86 (62-127)	0.298
Fibrinogen, g/L (range)	1.65 (0.68-3.05)	1.67 (0.68-2.44)	1.65 (1.20-3.05)	0.614
Triglycerides, mmol/L (range)	2.54 (0.51-11.42)	3.03 (1.74-3.55)	1.77 (0.51-11.42)	0.193
AST, U/L (range)	58.4 (16.9-1,435.7)	54.5 (16.9-1,435.7)	63.4 (33.7-452.9)	0.345
ALT, U/L (range)	47.6 (10.7-680.6)	28.2 (10.7-680.6)	59.0 (19.7-480.2)	0.102
IFN-γ, increase (fold)	12.3 (1.65-246.2)	13.9 (2.6-246.2)	8.1 (1.6-120.3)	0.382
sCD25, increase (fold)	3.0 (0.5-16.6)	4.4 (0.6-16.6)	1.7 (0.5-12.2)	0.169
Ferritin, increase (fold)	3.4 (0.1-39.8)	3.5 (0.1-22.1)	3.3 (0.2-39.8)	0.776
CNS involvement, N (%)	11 (52.4)	5 (55.6)	6 (50.0)	0.801

The baseline values of IFN-γ, ferritin and soluble CD25 were described as "increase (fold)", which was calculated based on the upper limits of reference range (8 pg/mL, 500 μg/L and 6,400 pg/mL). ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CNS: central nervous system; IFN-γ: interferon-γ; sCD25: soluble CD25. Laboratory clinical reference range: AST ≤40 U/L; ALT ≤40U/L; IFN-γ ≤8 pg/mL; ferritin ≤500 μg/L; soluble CD25 ≤6,400 pg/mL.

disease. The other details for previous HLH treatment were described in the *Online Supplementary Table S2*.

Efficacy

Throughout the treatment, one (4.8%) patient received RUX monotherapy, seven (33.3%) patients received RUX plus methylprednisolone, thirteen (61.9%) patients received RUX plus methylprednisolone plus etoposide. Detailed treatment information for each patient is shown in the *Online Supplementary Table S3*.

Clinical outcome of the patients is summarized in Table 2. Within the first 8 weeks, all patients had an objective response, of which 19 (90.5%) patients achieved CR and two (9.5%) patients achieved PR as a best response. Eight (42.1%) patients relapsed after achieving CR, and the triggers for relapse in four (50.0%) patients were infections and in four (50.0%) patients were unknown factors. Seventeen (81.0%) patients received HSCT, and the duration from RUX-based therapy to HSCT was 106.6±50.8 days.

Among 17 patients received HSCT, 13 (76.5%) patients had a CR, three (17.6%) patients had a PR, one (5.9%) patient had HLH reactivation at the time of HSCT. Seventeen (100%) patients got CR after HSCT. Fifteen (88.2%) patients were alive post-HSCT, while two (11.8%) patients died more than 1 year after HSCT. Two patients with XIAP gene mutation did not undergo HSCT at the discretion of their physicians and they had sustained control of disease over 1 year after treatment was stopped. Four (19.0%) patients died, two (50.0%) of whom died before HSCT due to persistent HLH activation and two (50.0%) of whom died after HSCT due to severe graft-*versus*-host disease (GvHD). Of note, both patients died before HSCT had CNS symptoms as the initial presentation of disease reactivation.

In addition, we would like to highlight that serum levels of interleukin-6 and IFN-γ decreased rapidly and significantly during treatment (*Online Supplementary Figure S2*), providing further evidence of the effectiveness of the RUX-based regimen.

Survival

All patients were followed up to date of death or October 1, 2022 (time of data cutoff), with a mean follow-up of 1.4±0.7 years. Survival to HSCT and overall survival are shown in Figure 1. At the last follow up, 17 (81.0%) patients were alive with a 1-year cumulative probability of survival of 90.5% (95% confidence interval [CI]: 84.1- 96.9). For previously treated patients, ten (83.3%) patients were alive with an estimated 1-year survival of 91.7% (95% CI: 82.7-99.7). For previously untreated patients, seven (77.8%) patients were alive with an estimated 1-year survival of 88.9% (95% CI: 78.4-99.4) (*Online Supplementary Figure S3*).

Etoposide dose intensity and cumulative glucocorticoid dose

Dose intensity of chemotherapy in the duration of waiting for HSCT was a subject of intense scrutiny. Given etoposide was the most predominant chemotherapy drug for our patients, we calculated the dose of etoposide of every patient and compared it to the dose according to HLH-2004 regimen under the same duration of waiting for HSCT. Three (33.3%) patients in the previously untreated

Table 2. Clinical outcome.

Outcome	Total N=21	Previously untreated N=9	Previously treated N=12	*P*
Duration of follow-up in years, mean ± SD	1.4 ± 0.7	1.1 ± 0.6	1.6 ± 0.8	0.095
Achieve CR within the first 8 weeks of therapy, N (%) Relapse, N (%)	19 (90.5) 8 (42.1)	8 (88.9) 3 (37.5)	11 (91.7) 5 (45.5)	0.368 0.914
HSCT, N (%)	17 (81.0)	7 (77.8)	10 (83.3)	0.811
Duration in days from RUX therapy to HSCT, mean ± SD*	106.6 ± 50.8	102.1 ± 33.3	109.7 ± 61.9	0.883
Response at the time of HSCT,* N (%) CR PR Active	 13 (76.5) 3 (17.6) 1 (5.9)	 6 (85.7) 1 (14.3) 0 (0.0)	 7 (70.0) 2 (20.0) 1 (10.0)	0.635
Death, N (%) Death before HSCT due to HLH	4 (19.0) 2 (9.5)	2 (22.2) 1 (11.1)	2 (16.7) 1 (8.3)	0.748 0.830
Death after HSCT, N (%)	2 (9.5)	1 (14.3)	1 (10.0)	0.787

*17 patients who underwent HSCT were included for analysis. HSCT: hematopoietic stem cell transplantation; CR: complete response; PR: partial response; SD: standard deviation; HLH: hemophagocytic lymphohistiocytosis.

group and five (41.7%) patients in previously treated group received zero doses of etoposide. Totally, eight (38.1%) patients received zero doses of etoposide during the during the whole treatment. Under the same waiting time for HSCT, patients treated by RUX-based regimen might receive less doses of etoposide than that of the patients treated by HLH-2004 regimen (Figure 2), suggesting that RUX-based regimen had the potential to reduce chemotherapy intensity.

Likewise, we calculated the cumulative dose of glucocorticoids of every patient. One (4.8%) patient received 0 mg of glucocorticoids during treatment. Under the same waiting time for HSCT, patients treated by RUX-based regimen might receive lower cumulative dose of glucocorticoids than patients treated according to the HLH-2004 regimen (*Online Supplementary Figure S4*), suggesting that RUX-based regimen allows for a reduction in cumulative glucocorticoid dosing in pHLH patients.

Safety

AE were summarized in Table 3. Overall, patients tolerated RUX-based treatment well and most AE were grade 1/2. Grade 3/4 AE that observed most frequently were hematologic AE, including anemia (23.8%), thrombocytopenia

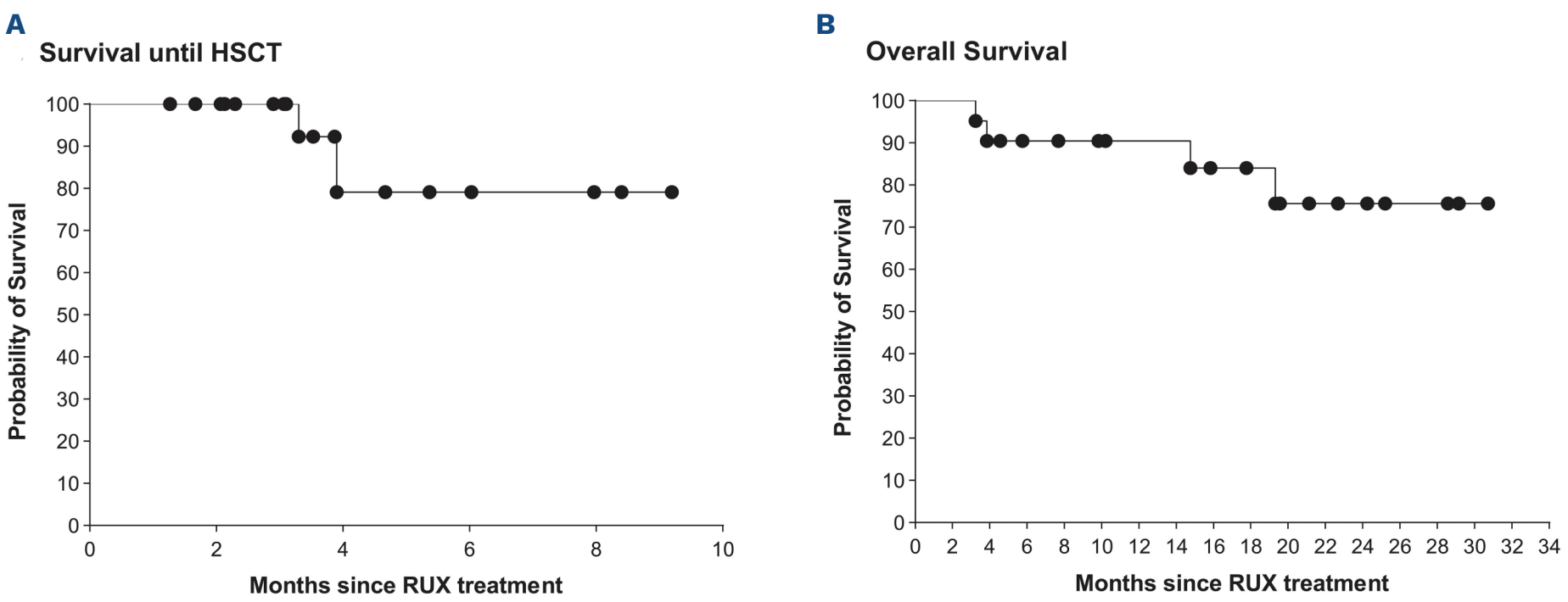

Figure 1. Kaplan-Meier estimates of survival. (A) Survival until hematopoietic stem cell transplantation (HSCT). Two patients with *XIAP* genetic mutation didn't receive HSCT were excluded from analyses. (B) Overall survival. RUX: ruxolitinib.

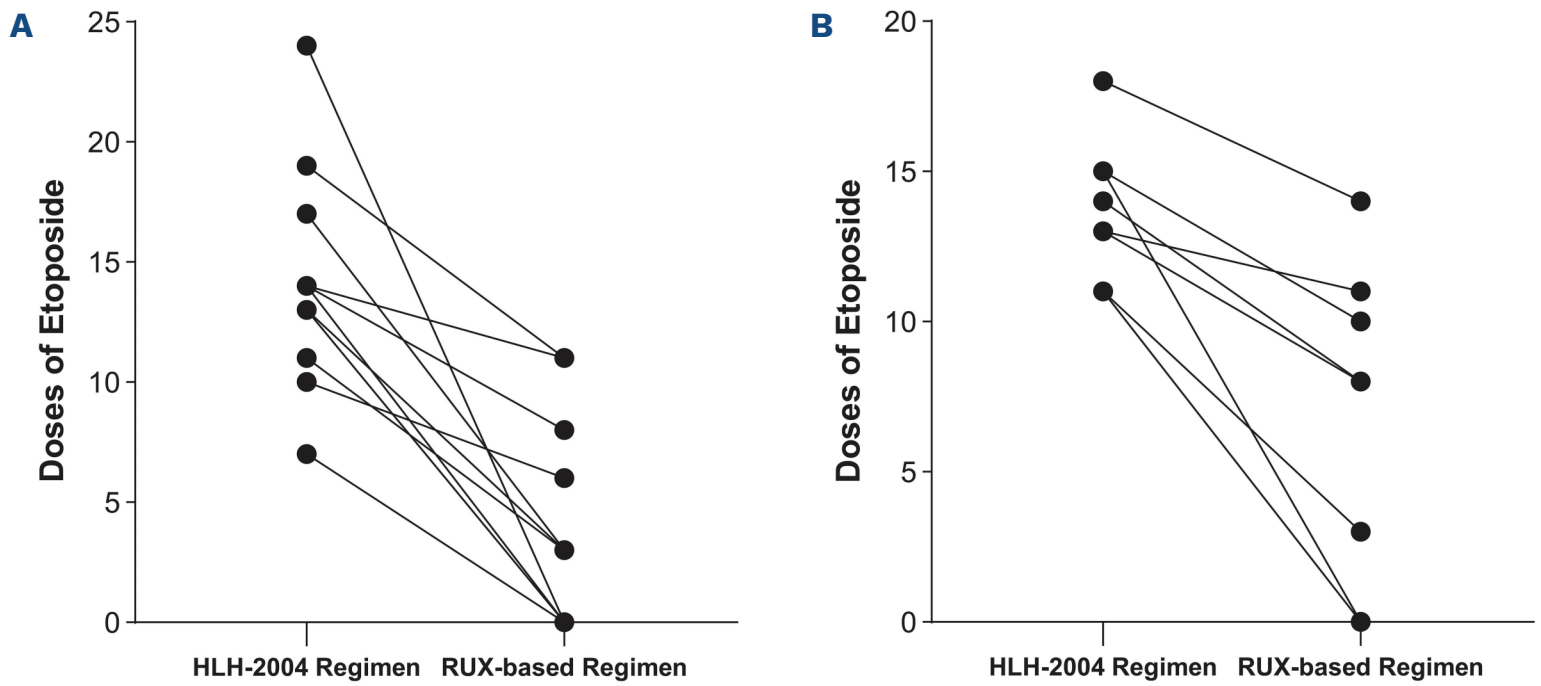

Figure 2. Patients treated by RUX-based regimen received reduced intensity of etoposide chemotherapy. (A) Previously treated patients. (B) Previously untreated patients (at the last follow up, 2 patients with *XIAP* genetic mutation didn't receive hematopoietic stem cell transplantation [HSCT] and their disease was controlled well over more than 1 year after the discontinuation of ruxolitinib [RUX]). After discontinuation of RUX, they didn't receive chemotherapy, so we only calculated the expected etoposide doses of HLH-2004 regimen in the RUX treatment duration). HLH: hemophagocytic lymphohistiocytosis.

(23.8%), neutropenia (33.3%) and myelosuppression (33.3%). One patient had grade 3 pancreatic damage and was treated with somatostatin without RUX discontinuation. After about 3 weeks of treatment, her pancreatitis was resolved. One patient was diagnosed with pulmonary tuberculosis and received antituberculosis therapy with RUX discontinuation. After 6 months of treatment, his tuberculosis was resolved. Among eight patients who did not receive etoposide chemotherapy, apart from grade 3 anemia observed in two (25.0) patients, no other grade 3/4 AE were observed. Of note, AE might be caused by RUX, chemotherapy drugs, HLH activation and co-existing conditions of them.

Discussion

PHLH is a rare and life-threating disorder characterized by hyperinflammation and immune dysregulation. Currently, the primary goal of therapy for pHLH patients is stably controlling the disease in order to perform HSCT, the only curative therapy.[5] In this study, we presented the efficacy and safety of RUX-based regimen in children with pHLH. To the best of our knowledge, this is the first cohort study demonstrating the clinical benefits of treating pHLH patients with RUX-based regimen. At the last follow-up, 17 (81.0%) patients were alive with a 1-year overall survival of 90.5% (95% CI: 84.1-96.9) and 17 (81.0%) patients received HSCT. Interestingly, our results indicated patients treated by RUX-based therapy received relative lower intensity of etoposide, suggesting the potential of RUX-based regimen to help patients reduce chemotherapy intensity.

CNS involvement is a portion of systemic immune response in HLH.[22] During the period of HLH treatment, frequent reactivation within CNS could occur independent of or concomitant with systemic relapses, which may be associated with the high risk of mortality.[23] Up to now, there have been no clinical trials focusing specifically on CNS involvement in HLH patients. Currently, intrathecal treatment with corticosteroids and methotrexate is the standard care for CNS symptoms and may have beneficial effects.[24] Results of an animal experiments indicated that RUX could penetrate the blood brain barrier of mice and RUX therapy could reduce CNS involvement in the *Rab27a*$^{-/-}$ mice, but these findings haven't been confirmed in human patients.[13,25] In this study, all patients with CNS involvement received intrathecal therapy and RUX treatment. However, two patients with CNS-HLH died due to disease reactivation with somnolence and coma as the first symptoms before undergoing HSCT. Two patients achieved PR but not CR as a best response because CNS involvement could not be completely remitted. Four patients with CNS involvement relapsed after achieving CR, of which three patients had CNS symptoms when the disease relapsed. These observations suggest RUX is probably not an ideal drug for CNS involvement and more effective treatments are needed. There is also evidence for the importance of HSCT in CNS involvement. Results from a retrospective study of 18 patients in a single center indicated immediate HSCT may be beneficial even if there is active disease.[26,27] Given the long waiting time for acceptable donors, physicians have to consider other treatments for CNS-HLH. Thus, the most plausible intervention for CNS involvement in pHLH pa-

Table 3. Possible adverse event.*

Outcome	Any grade	Grade ≥3
Hematologic AE, N (%)		
Anemia	15 (71.4)	5 (23.8)
Thrombocytopenia	13 (61.9)	5 (23.8)
Neutropenia	15 (71.4)	7 (33.3)
Myelosuppression	14 (66.7)	7 (33.3)
Non-hematologic abnormalities, N (%)		
Constipation	6 (28.6)	0
Pancreatic damage	7 (33.3)	1 (4.8)
Rash	4 (19.0)	0
Diarrhea	4 (19.0)	0
Liver damage	5 (23.8)	0
Sweating	1 (4.8)	0
Gastritis	1 (4.8)	0
Secondary infection	3 (14.3)	1 (4.8)
Heart damage	3 (14.3)	0
Kidney damage	3 (14.3)	0
Gastrointestinal hemorrhage	3 (14.3)	1 (4.8)

A part of patients had more than 1 adverse event (AE). *AE might be caused by drugs, hemophagocytic lymphohistiocytosis activation and co-existing conditions of them.

tients warrants further exploration.

During HLH treatment, the high dosage of chemotherapy drugs remains an important concern. Etoposide-based HLH-1994 and HLH-2004 regimens are the most frequently used chemotherapy regimens to treat HLH and the treatment-related morbidity and potential mortality has been observed.[28] Possible AE from the therapy, especially etoposide, include secondary infections, hepatic dysfunction, myelotoxicity and secondary malignancies. Moreover, the toxic effects will be increased with reintensification of etoposide among patients with HLH flares.[5,9] Therefore, alternative regimens with less toxicity are urgently needed. According to the recommendations provided by HLH steering committee of the histiocyte society for the use of etoposide-based therapy for the treatment of HLH, treatment may have to be individualized depending on the clinical context, and the drug doses and/or dosing intervals can be altered.[29] Remarkably, our results suggest that RUX-based regimen have good efficacy and the potential to reduce chemotherapy intensity. pHLH is known to be characterized by frequent reactivations.[24] However, for most patients in this study, the disease was controlled rapidly by treated with RUX-based regimen and parts of them had well-controlled disease persistently without HLH reactivation after achieving CR. Moreover, results of our previous studies demonstrated RUX had a quick effect on HLH because all responding patients achieved the first response to RUX monotherapy within 3 days.[15] Therefore, RUX-based regimen or RUX-contained regimen are worth considering to minimize the toxicity of chemotherapy when making treatment plans for HLH patients.

Management and treatment for pHLH patients with *XIAP* gene mutation may be different. In a study from Europe, 54 HLH patients with X-linked inhibitor of apoptosis deficiency did not undergo HSCT and 49 of them survived at a median time of 4 years after diagnosis.[30] In our study, two patients with pathogenic genetic mutations of *XIAP* did not receive HSCT and have stopped the drugs for more than 1 year. They survived without disease activation until the last follow-up. For these patients, the most beneficial treatment decisions should be made according to the clinical features.

There are several limitations in this study. First, this is a retrospective study and there could be sources of bias including confounding bias, elective bias and observational bias. Therefore, our results of this study need to be further validated by well-designed, prospective study. Second, this study included patients who had received prior treatment that had either been ineffective in achieving the desired outcome or had caused intolerable side effects. However, there is still no evidence of worse prognosis for these patients and their clinical characteristics and outcome were not significantly different with initially treated patients. Third, all patients included in this study were of Chinese origin, and the most highly mutated gene was *UNC13D*, which is different from studies conducted by the Histiocyte Society.[7,8] Thus, results from this study may not be applicable to other pHLH populations. Fourth, it is important to acknowledge that the median follow-up duration in this study was relatively short, spanning only 1.4 years, and therefore, the long-term outcomes of survival post-HSCT remain unclear. Nevertheless, previous research indicates pHLH patients who had CR at HSCT may have a more favorable long-term overall survival than those with PR.[31] Notably, 76.5% of patients in this study had CR at the time of HSCT, suggesting that the use of RUX-based regimen as a pre-HSCT therapy may hold great promise for pHLH patients.

In summary, our study demonstrates that for children with pHLH, RUX-based regimen was effective and safe and could be used as a bridge to HSCT.

Disclosures

No conflicts of interest to disclose.

Contributions

RZ, JG and QZ conceptualized and designed the study and drafted the initial manuscript. ZGL and TYW conceptualized and designed the study and reviewed and revised the manuscript. AW, TZ, WQW and CXZ collected the data, carried out the initial analyses, and reviewed and revised the manuscript. HHM, DW, YZZ, HYL, MQQ and JY conceptualized and designed the study, coordinated and supervised the data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data-sharing statement

Original data and protocols are available to other investigators upon request by contacting the corresponding author.

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