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Research Article

Low dose ruxolitinib plus HLH-94 protocol: A potential choice for secondary HLH ☆

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is an immune-mediated syndrome resulting in cytokine storm. The uncontrolled cytokine storm leads to significant tissue damage and potentially life-threatening multiorgan failure. Conventional first-line treatment for HLH included HLH-94 protocol or HLH-2004 protocol. However, up to 30% of patients do not respond to first-line therapy. We reported 3 cases of secondary HLH/macrophage activation syndrome which were caused by lymphoma (2 cases) and adult-onset still's disease. They received low dose ruxolitinib plus HLH-94 protocol, and had rapid response to treatment without obvious adverse effects. Following the treatment, there was improvement seen in several disease markers, including fever, fibrinogen, serum ferritin, and liver function tests. Our report indicated that treatment with low dose ruxolitinib plus HLH-94 protocol might be a potential choice for secondary HLH, and clinical trials warrants to be further investigated in this treatment regimen.

Introduction

Hemophagocytic syndrome (hemophagocytic lymphohistiocytosis [HLH]) is a life-threatening clinical syndrome that is characterized by fever, organomegaly, and pancytopenia [1]. This clinical syndrome can be classified as primary HLH and secondary HLH. Primary HLH is thought to be the result of genetic defects. Secondary HLH may be acquired with infectious, neoplastic, autoinflammatory, autoimmune, and immunodeficiency etiologies. The pathogenesis of HLH is largely unknown yet characterized by impaired natural killer and cytotoxic T-cell function, hyperactivation of antigen presenting cells and T cells, and an uncontrolled response of proinflammatory cytokines (cytokine storm) which leads to tissue damage and progressive systemic organ failure [1].

Conventional therapy for HLH consists of immunomodulatory agents, such as corticosteroids, etoposide, cyclosporine, and intravenous immunoglobulin. Based on HLH-94 protocol the outcome is able to achieve 5-year survival from 5% up to more than 50% [2]. HLH-2004 added CSA to the initial treatment phase for controlling cytokine storm and T-cell proliferation. Up to 30% of patients whom do not respond to first-line therapy may require alternative regimens including other immunosuppressive chemotherapy and/or biologic agents [3]. How to quickly control the cytokine storm that threaten life? Das et al give us a good answer. They report their results from the use of the Janus kinase 1/2 (JAK1/2) inhibitor ruxolitinib in murine models of HLH, and the HLH-sibling macrophage activation syndrome (MAS). Their results showed ruxolitinib was a promising option for treating HLH [4]. We report 3 cases of secondary HLH (2 cases of secondary HLH associated with lymphoma, 1 case of HLH-sibling MAS) caused by adult-onset still's disease (AOSD). These results showed patients responded quickly to the treatment of ruxolitinib plus HLH-94protocol.

Case report

Case 1

A previously healthy 24-year-old man was brought to the department of hepatology with recurrent fever, icterus for 6 days on July 22, 2017. The laboratory data revealed abnormal liver function studies with aspartate aminotransferase (AST) of 181.3 units/L (normal:<40 units/L), alanine aminotransferase (ALT) of 233.8 units/L (normal:<41 units/L), total bilirubin was 135.3 umol/L(3.4-20 umol/L). The laboratory data also revealed leukopenia [1.95×10^9/L (normal: 3.5-9.5 $\times 10^9$/L)], neutropenia

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[0.48×10^9/L (normal: 1.8-6.3 $\times 10^9$/L)], and thrombocytopenia [97×10^9/L (normal: 100-300 $\times 10^9$/L)] with normal level of hemoglobin and normal coagulation function. Erythrocyte sedimentation rate was normal and C-reactive protein levels were elevated [46.9mg/L (normal:<10)]. The level of interleukin 6 increased to 93pg/ml(normal:<7). Doppler ultrasound of his abdomen showed moderate splenomegaly. Computed tomography of his chest was unremarkable. After admission, he was empirically started on meropenem and vancomycin for febrile neutropenia and treatment of liver protection. Fever was not controlled, and the patient developed into pancytopenia. On August 1st, the laboratory data revealed leukopenia (1.74×10^9/L), thrombocytopenia (29×10^9/L), decreased level of hemoglobin (HB) [90 g/L (normal: 120-160)] and decreased level of fibrinogen [1.1 g/L (normal: 2-4)]. His ferritin level was greater than 50,000 ug/L (normal:30-400), and interleukin 6 level was more than 597pg/ml. Blood cultures were negative. An initial autoimmune workup revealed normality. Viral workup, by IgM antibody and viral titers, was negative for human immunodeficiency virus, hepatitis A, B, and C, herpes simplex virus, herpes zoster, parvovirus, cytomegalovirus, and adenovirus. Epstein-Barr virus (EBV)-DNA copy number is increasing, EBV-DNA in peripheral blood mononuclear cell (PBMC) is 2.77×10^5/L(normal:500/L), EBV-DNA in blood plasma is 8.46×10^3/L(normal:500/L). The patient was diagnosed as HLH and was transferred to the division of hematology. He received bone marrow evaluation, bone marrow aspiration revealed there were 6% prolymphocyte like cells .Flow cytometry of bone marrow revealed that 7.4% nucleated cells were abnormal immunophenotype NK cells (CD45bri+, CD56bri+, Ki67+, CD16-, CD57-, cCD3-, CD158b-, CD158ah-, TCR$\gamma\delta$-, TCR$\alpha\beta$-). Perforin and CD107a tests showed normality. Finally, he was diagnosed as EBV-positive aggressive NK cell leukemia(ANKL) [5] and secondary HLH according to HLH diagnostic criteria [17], then he immediately received the treatment according to according to HLH-94 treatment protocol 4 on August 2nd (Table 1). After 7 days of initial treatment, his symptoms didn't improve, and this patient received treatment of plasmapheresis(removal of 2500 ml of plasma) and ruxolitinib(Jakafi) (5mg bid). After 6 days of ruxolitinib treatment the patient had no fever, his total bilirubin dropped to 58 umol/L and level of fibrinogen became normalized(Fig. 1). After 2 weeks of ruxolitinib treatment, the level of Ferritin began to drop (Fig. 1). Then the patient received chemotherapy of Pegaspargase +GemOx protocol (Gemcitabine 1000mg/m^2 d1 d15, oxaliplatin 100mg/m^2 d1, d15, Pegaspargase2500u/m^2 d16) (Table 1). After 30 days of ruxolitinib treatment his ferritin level dropped to 2762 ug/L, both of EBV-DNA copy number in PBMC and blood plasma were negative. The level of interleukin 6 decreased to 56pg/ml(normal:<7). Flow cytometry did not detect aggressive NK cell. The patient was discharged with continuous oral 30mg/d prednisone. One month later, he was brought to local hospital with high fever and pancytopenia again. Because of financial difficulties, he gave up all treatment and died 3 days after admission.

Table 1
Summary treatment of the patient.

Drug	Usage	
Case 1. Treatment according to HLH-94 treatment protocol and GemOx protocol		
Dexamethasone	10 mg/m^2	D 1-14,
	5 mg/m^2	D 15-28,
	2.5 mg/m^2	After 1 month until relapse
Etoposide	150 mg/m^2	D 1, 4, 8 and 11
Plasmapheresis	2500 ml	D 7
Ruxolitinib	5 mg bid	D 7-32,
	5 mg qd	D 33-43
Gemcitabine	1000 mg/m^2	D 15, 28,
Oxaliplatin	100 mg/m^2	D 15, 28
Pegaspargase	2500 units/m^2	D 16
Case 2. Treatment according to HLH-94 treatment protocol		
Dexamethasone	10 mg/m^2	D 1-14
	5 mg/m^2	D 15-28,
	2.5 mg/m^2	After 1 month, slow reduction till maintenance treatment of 10mg prednisone
Etoposide	100 mg/m^2	D 1, 4
Ruxolitinib	5 mg bid	D 1-25
	5 mg qd	D 26-35
Case 3. Treatment according to HLH-94 treatment protocol and GemOx protocol		
Dexamethasone	10 mg/m^2	D 1-14,
	5 mg/m^2	D 15-28,
	2.5 mg/m^2	After 1 month for maintenance treatment
Etoposide	150 mg/m^2	D 1, 4, 8 and 11
Ruxolitinib	5 mg bid	D 1-25
	5 mg qd	D 26-35
Gemcitabine	1000 mg/m^2	D 15, 28,
Oxaliplatin	100 mg/m^2	D 15, 28
Pegaspargase	2500 units/m^2	D 16

Case 2

A previously healthy 52-year-old female was admitted to the fever ward in our hospital on October 5th, 2017, with congestive erythema of left lower extremity and waist for 1-month, recurrent fever with myalgia and sore throat for 16 days. Physical examination revealed body temperature of 39.5°C, throat congestion, congestive erythema of left lower extremity and waist without hepatosplenomegaly and superficial lymph node enlargement. The laboratory data also revealed leukocytosis (17.62×10^9/L) with normal level of hemoglobin and blood platelet count. Coagulation detection showed normal coagulation function. Erythrocyte sedimentation rate and C-reactive protein levels were increasing. The level of interleukin 6 increased to 97.58pg/ml. Her ferritin level was 2589 ug/L. Doppler ultrasound of her abdomen and computed tomography of her chest were unremarkable. Blood cultures were negative. An initial autoimmune workup revealed normality. Viral workup, by IgM antibody and viral titers, was negative for human immunodeficiency virus, hepatitis A, B, and C, herpes simplex virus, herpes zoster, parvovirus, cytomegalovirus, and adenovirus. EBV-DNA in PBMC and plasma was normal. After admission, she was empirically started on meropenem and vancomycin. Fever was not controlled, and the patient had anemia and thrombocytopenia. The patient was transferred to the division of hematology on October 20th. The bone marrow cytomorphologic examination showed there was hemophagocytosis, and flow cytometric analysis showed there was no abnormal clone. The laboratory data revealed abnormal liver function studies with AST of 274 units/L, ALT of 152 units/L. The laboratory data revealed leukocytosis (23.64×10^9/L), anemia (94g/L) and thrombocytopenia (54×10^9/L). Coagulation detection showed decreased level of fibrinogen (0.87g/L). Her ferritin level was 44049 ug/L. According to her clinical manifestations and laboratory tests, she was diagnosed HLH. In view of previous ruxolitinib experience, she immediately received the treatment ruxolitinib and amended HLH-94 protocol (Table 1). Four days after treatment, her fever was controlled, the ferritin level began to fall rapidly, and the fibrinogen level began to rise (Fig. 1). And 1 week later, the flow cytometry of bone marrow showed there was no abnormal clone. Finally, she was diagnosed with secondary HLH caused by AOSD [16], and the etoposide was not used after 2 dosages. After 2 weeks of treatment, the laboratory data showed normal liver function, normal coagulation function (Fig. 1), normal blood platelet counts and leukocytes. During the treatment she had dry mouth and dry eyes. Ophthalmology examination showed xerophthalmia, and ECT findings showed severely impaired func-

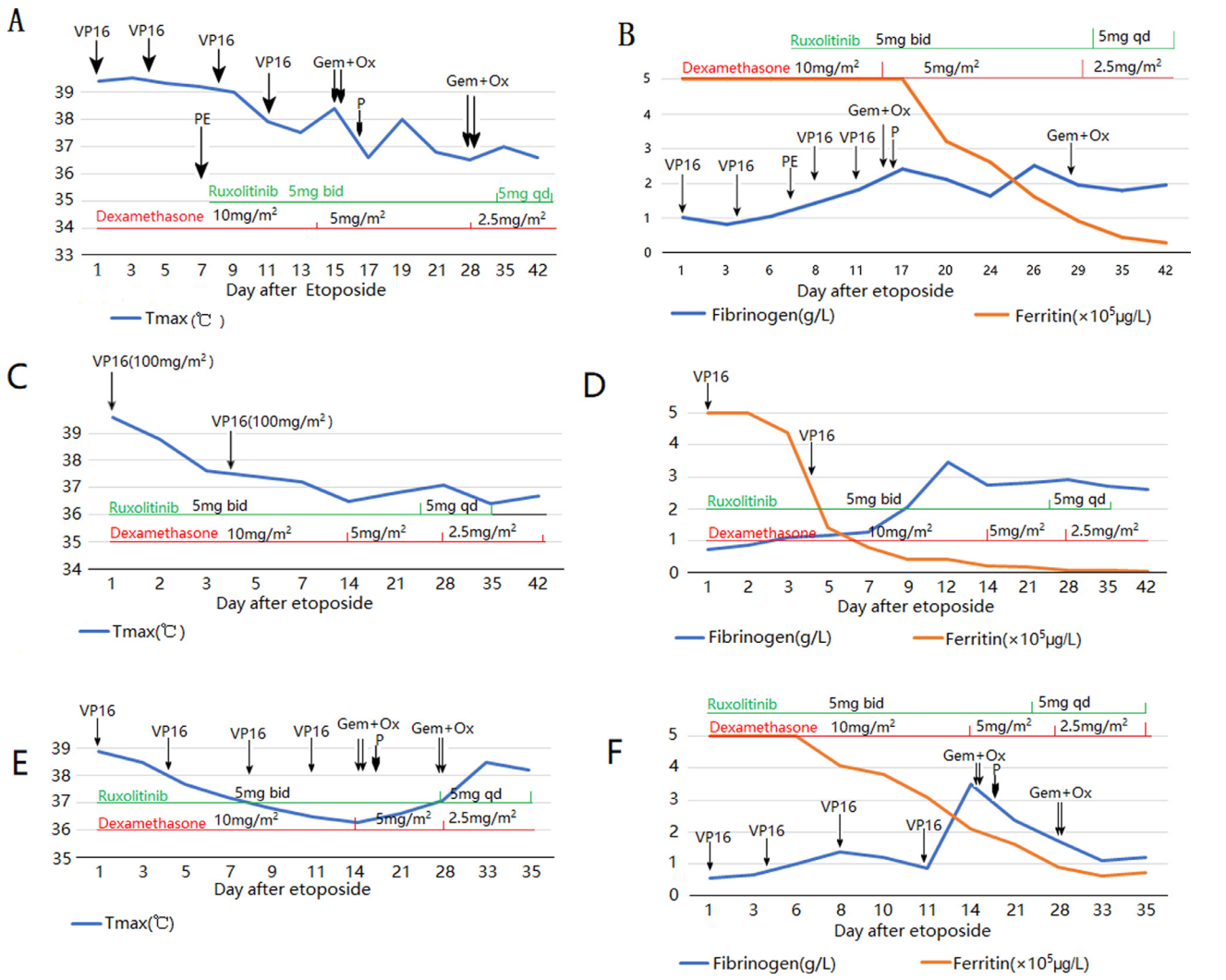

Fig. 1. Patient's laboratory and clinical response to treatment after etoposide and dexamethasone treatment. (A) Daily maximum temperature curve (°C) for case 1. (B) The curve of fibrinogen and ferritin for case 1. (C) Daily maximum temperature curve (°C) for case 2. (D) The curve of fibrinogen and ferritin for case 2. (E) Daily maximum temperature curve (°C) for case 3. (F) The curve of fibrinogen and ferritin for case 3. VP16 = etoposide; Gem = gemcitabine; Ox = oxaliplatin; P = Pegaspargase; PE = plasmapheresis

tion of bilateral submandibular gland. Result of lip biopsy did not meet the diagnostic criteria of sicca syndrome. She left hospital with oral prednisone, and prednisone was reduced slowly. Now she takes 10 mg prednisone for maintenance treatment and laboratory tests showed normal results.

Case 3

A 45-year-old woman was brought to the department of hematology with recurrent fever for 10 days on January 2nd, 2018. On January 2015, the patient was diagnosed as peripheral T-cell lymphoma by fine needle aspiration biopsy of retroperitoneal mass. Then she received 6 cycles chemotherapy of CHOP-like regimens. After admission, she received medical examination. The laboratory examination revealed abnormal liver function studies with AST of 161 units/L, ALT of 343 units/L, high level glycerin trilaurate [5.48 mmol/L (normal: <1.7)], hyponatremia [125 mmol/L (normal: 136-145)].The laboratory data also revealed leukopenia (0.8×10^9/L), thrombocytopenia (31×10^9/L) with decreased level of hemoglobin (93g/L) and decreased level of fibrinogen (1.16 g/L). Her ferritin level was greater than 50,000 ug/L. Computed tomography (CT) of her chest showed normality. Abdominal enhanced CT scan showed that retroperitoneal enlarged lymph nodes were in accord with recurrence of lymphoma. She received bone marrow puncture, bone marrow aspiration revealed there were 7% immature lymphocyte. Flow cytometric analysis of bone marrow revealed that 3.4% nucleated cells were abnormal immunophenotype T cells (CD45bri+, CD3dim+, CD2bri+, CD33dim+, CD117dim+, HLA-DRbri+, TCR$\alpha\beta$+, cCD3-, CD4-, CD7-, CD5-, CD56-, CD30-, CD16-, CD15-, CD64-, CD14-, CD34-, CD13-, TCR $\gamma\delta$-, CD22-, Cmpo-, cCD79a-, partly CD8+, KI67 55.6%). She was diagnosed with relapse of peripheral T-cell lymphoma and secondary HLH. Given previous experience from case 1, she immediately received the treatment ruxolitinib and amended HLH-94 protocol (Table 1). Three days after treatment, her fever was controlled. Two weeks later, the level of fibrinogen and liver function restored to normal range, and her ferritin level dropped to 21009 ug/L (Fig. 1). Then the patient received chemotherapy of Pegaspargase +GemOx protocol (Gemcitabine 1000 mg/m^2 d1 d15, oxaliplatin 100 mg/m^2 d1 d15, Pegaspargase2500 u/m^2 d16) (Table 1). After 30 days of treatment, she developed a fever again, was diagnosed with having lung infection (CMV+fungi) according to her lung CT, whole blood CMV-DNA test, and plasma GM test. The test of minimal residual disease in bone marrow by flow cytometric analysis the patients showed

that there were 0.3% abnormal immunophenotype T cells. The patient went back to the local hospital with sustained treatment of ganciclovir and amphotericin. Two weeks after discharge, she died from failure of respiration and DIC.

Discussion

HLH/MAS are hyperinflammatory disorders that have many characteristics which is related to cytokine storm-associated symptoms, such as sepsis and systemic inflammatory response syndrome. These diseases are lack of optimal treatment due to largely unknown pathogenesis [6,7]. Although HLH patients treated with HLH-1994 protocol had achieved a 5-year survival rate of 54%, there was a third of the patients not achieving a significant response. The cytokine storm has pathogenically influence on the development of the major clinical and laboratory features of HLH and leads to tissue damage and progressive systemic organ failure [8]. The cytokine storm in HLH is also quite licentiousness: IFN-γ, IL-1, IL-4, IL-6, IL-10, IL-18, TNF-α, and other critical proinflammatory cytokines are responsible for inflammation-driven tissue damage. The key for HLH is rapidly controlling the cytokine storm. The results from HLH murine model treated with ruxolitinib indicate that ruxolitinib may be a reasonable choice for HLH [4]. We reported 3 cases of HLH: 2 cases were secondary HLH caused by ANKL and T-lymphoma, the other case was secondary HLH/MAS caused by AOSD. The patients had prompt response to ruxolitinib plus HLH-94 in 1 week. The initial manifestation of the treatment response was rapid control of fever, then improvement of abnormal coagulation and liver function. Improvement in secondary HLH/MAS gave a chance for further treatment of the disease.

Previous studies have shown that JAK1/2 inhibitor ruxolitinib reduced T-cell proliferation and inhibited proinflammatory cytokines. The cytokine profiles were changed after rats were applied with ruxolitinib, and significant change of cytokines including IL-1, IL-2, IL-4, IL-10, IFN-γ, and TNF-α [9]. Ruxolitinib abrogated the SLE plasma-induced monocyte cytokine signature, such as monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory protein-1β (Mip1β) and interleukin-1 receptor antagonist (IL-1RA) [10]. Acute graft versus host disease, another acute syndrome of inflammation, was reported to respond to ruxolitinib after the failure of corticosteroid treatment promptly, and ruxolitinib weakened differentiation of CD4(+) T cells into IFN-γ, and IL17A-producing cells and increased FoxP3(+) regulatory T cells [11]. Gain-of-function mutations in the human signal transducer and activator of transcription 1 (STAT1) cause immunodeficiency disease and autoimmune disease with impaired TH17 cell differentiation and exaggerated responsiveness to type I and II interferons. One case study showed ruxolitinib treatment reduced hyperresponsiveness to type I and II interferons, normalized TH1 and follicular T helper cell responses, improved TH17 differentiation, cured immunodeficiency-induced mucocutaneous candidiasis, and maintained remission of immune-mediated cytopenias [12]. Ruxolitinib also ameliorated the damage of liver by dampening the overproduction of proinflammatory cytokines (TNF-α, IL-1β, IFN-γ, IL-23, and IL-17A) [13]. Current studies have shown that ruxolitinib might be a potential choice for treatment of immune-mediated inflammation syndromes.

Recently, there were 2 case reports on ruxolitinib for secondary HLH [14,15]. One case is a 71-year-old woman with secondary HLH caused by rheumatoid arthritis, she only received ruxolitinib treatment (10 mg p.o. twice daily) [14]. There were no immediate adverse effects, and her shock, mental status, and respiratory failure improved within 2 days of initiating therapy. Another case is a 38-year-old woman with secondary HLH caused by EBV infection. He received higher dose of ruxolitinib (20 mg p.o. twice daily) after 25 days of treatments with HLH-94 protocol plus Rituximab, treatment response appeared on the fourth day of ruxolitinib treatment [15]. Broglie et al reported 1 case of refractory HLH treated with ruxolitinib [18]. The patient received ruxolitinib (2.5 mg p.o. twice daily) after HLH-94 plus anakinra treatment failed. In a week, the patient's body temperature was back to normal and Ferritin began to drop. There were no accepted diagnostic criteria for refractory HLH. It was recognized that the sign of refractory HLH was no response of biomarkers (eg, ferritin/fever/fibrinogen/transaminases) at 2 weeks. In consideration of the harm of cytokine storm it is necessary to promptly control the cytokine storm. We added treatment of ruxolitinib and plasmapheresis; although the first case did not meet the standard for refractory HLH. As other reports, the condition of the patient improved promptly. Whether the patient's improvement was due to HLH-94+ruxolitinib or in combination with plasmapheresis is uncertain. However, the patient did not show clinical deterioration without continuing the plasmapheresis. The key of successful HLH treatment was to control cytokine storm. For the control of cytokine storm, these 3 methods (HLH-94, ruxolitinib, and plasmapheresis) had different mechanisms of action, and the results might have synergistic effect. The plasmapheresis is not used routinely in consideration of the high cost and high risk.

Two other cases of secondary HLH caused by lymphoma and AOSD also had prompt responses to treatment of HLH-94+ low dose ruxolitinib (5 mg p.o. twice daily). Standard treatment of MAS is high dose methylprednisolone 30 mg/kg for 3 days followed by 2 to 3 mg/kg/day in 2 to 4 divided doses [19]. MAS bears great similarity to HLH. The diagnosis of MAS often lags behind the HLH for patients without AOSD history. When the patient without the history of autoimmune diseases had characteristics of HLH first, treatment of HLH-94+ low dose ruxolitinib was a reasonable choice. The 3 patients had prompt responses without obvious related adverse effects. For HLH secondary to T-NHL, controlling HLH with less adverse effects as soon as possible was the reasonable choice for treatment, and this created conditions for NHL chemotherapy. We thought the ruxolitinib met the clinical needs. For the third patient, despite HLH and lymphoma was controlled, the infection led to final treatment failure. Infection was the adverse effect of ruxolitinib that physicians needed to focus on.

Conclusions

HLH is a severe and potentially fatal disease process. Although many pharmacologic agents are available, patients may not respond favorably to conventional options. Given the rapid improvement, ruxolitinib warrants further evaluation further in clinical trials as a targeted treatment for HLH.

Competing interests

No competing interests as defined by Molecular Medicine, or other interests that might be perceived to influence the results and discussion reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.seminhematol.2018.07.006.

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