Comment on: A pilot study of ruxolitinib as a front-line therapy for 12 children with secondary hemophagocytic lymphohistiocytosis

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Running Heads: Ruxolitinib therapy for HLH in children

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Abbreviations	Full term or phrase
HLH	hemophagocytic lymphohistiocytosis
CR	complete response
JAK	Janus kinase
EBV	Epstein-Barr virus
EFS	event-free survival

In a recent article in Haematologica, Zhang and colleagues highlighted the efficacy and safety of ruxolitinib and the possibility of ruxolitinib-based front-line therapy in pediatric patients with secondary hemophagocytic lymphohistiocytosis (HLH)[1]. The rapid recovery of clinical manifestations and normalization of clinical laboratory indexes demonstrated that ruxolitinib could serve as a potential front-line treatment option for secondary HLH in children, consequently reducing the toxicity compared to intense chemotherapy.

Although HLH-1994/2004 regimen has been recommended to the treatment of HLH in recent decades, there are still some patients who do not respond well or have intolerable side effects from conventional chemotherapies[2, 3]. To date, there are many case reports about the experiences of utilizing Janus kinase (JAK) 1/2 inhibitor, ruxolitinib, in the treatment of HLH[4, 5]. However, most of these cases involved adults, and few cases have been reported about the use of ruxolitinib in pediatric patients with HLH. The study firstly enrolled 12 children with HLH, and evaluated the safety and efficacy of ruxolitinib in pediatric patients. They found that the overall response rate of ruxolitinib was 83.3%, with 66.7% in complete response (CR). More importantly, no serious adverse effects were observed in this study, except for some grade 1-2

gastrointestinal adverse events (gastritis, nausea, and loss of appetite) in two patients. They also brought up a new idea that clinicians could attempt to utilize ruxolitinib first for approximately 3 days to determine the treatment response and sort applicable patients to avoid chemotherapy as possible. And they found that those patients who poorly responded to ruxolitinib after 3-7 days of treatment all responded well to the subsequent HLH-1994 protocol. HLH-1994/2004 regimen and ruxolitinib can be two complementary front-line therapy strategies, and further studies are warranted to testify this idea and sort the specific HLH group sensitive to ruxolitinib to guide effective treatment in the future.

Epstein-Barr virus (EBV)-associated HLH accounts for approximately 60% of all pediatric HLH patients in China, and most of those patients have a poor response to the standard treatment of HLH-1994/2004 and have a poor prognosis[6]. Moreover, current ongoing clinical trials studying the use of ruxolitinib in HLH patients have not yet enrolled the patients with (EBV)-associated HLH. The study enrolled 8 pediatric patients with HLH and found that the response rate of EBV-associated HLH patients was 100% and the CR rate was 75%, and EBV DNA load in plasma of all EBV-associated HLH patients decreased dramatically within one week. All of above suggested the great possibility of ruxolitinib for treating EBV-associated HLH, though the sample size was too small.

To truly improve the clinical treatment outcome for HLH in children, further trials will require a large cohort size, coherent eligibility criteria and dosing schedules to evaluate the safety and efficacy of ruxolitinib in treating HLH in children patients, especially EBV-associated HLH. Nonetheless, this reported pilot study made a major progress in managing HLH in children patients without traditional chemotherapy.

Conflict of Interest statement: The authors declared that they have no conflicts of interest to this work.

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