Expanding treatment options by selectively targeting the cytokine storm with ruxolitinib in primary hemophagocytic lymphohistiocytosis

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Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome characterized by uncontrolled activated cells of the lymphoid and mononuclear phagocytic system (MPS), leading to excessive cytokine production and systemic tissue and organ damage. Primary HLH patients require hematopoieitic stem cell transplantation (HSCT) of which survival figures depend on prior disease control. Despite advancements in its understanding and management, HLH remains a challenging condition with a significant mortality rate. However, recent clinical data has shed light on a potential breakthrough using the Janus kinase (JAK) inhibitor, ruxolitinib.

The immunopathophysiology of HLH is fascinating. Once triggered, normally self-regulating histiocytes remain activated and cause a cascade of inflammatory events eventually leading to an uncontrolled potentially fatal cytokine storm.[1] The basis for understanding the immunological mechanisms of HLH was laid by the demonstration of specific mutations in the perforine genes in primary HLH. Genetic defects in the perforine functions impair the function of cytotoxic $CD8^+$ lymphocytes and natural killer cells. These cells are paramount in the self-regulating feedback towards the activated MPS cells.[1] Regardless of the trigger, the final common pathway in HLH involves excessive cytokine release, particularly interleukin-6 (IL-6), IL-1β, IL-2, interferon-γ (IFN-γ), granulocyte-macrophage colony-stimulating factor and tumor necrosis factor-α, which further exacerbates the immune response and eventually leads to tissue damage[2] (Figure 1). Blocking the activated cells by inhibiting these cytokines theoretically might prevent these events. Ruxolitinib, a potent JAK1/2 inhibitor approved for myelofibrosis and polycythemia vera, has emerged as a potential therapeutic option for HLH by selectively inhibiting these stimulating and effector cytokines. Unlike traditional non-selective immunosuppression, ruxolitinib specifically targets JAK-STAT signaling, preserving the immune response against infections while dampening the destructive cytokine storm.[2]

So far only 17 primary HLH patients (of which some may involve overlapping cases) treated with ruxolitinib as salvage therapy have been described, mainly in case reports.[3] In this issue of Heamatologica Ge *et al.* retrospectively describe the largest cohort of primary HLH cases treated with ruxolitinib so far involving 21 children.[4] Most reported 5-year survival figures in comparable cohorts are between 60% and 70%, demonstrating the highest mortality rate in the first few months.[5,6] However, by adding ruxolitinib to the standard of care therapy to bridge time to HSCT Ge *et al.* observed a remarkable 1-year overall survival of 90.5%, higher than the about 65% in the aforementioned studies.[4-6] Additionally, this study highlights the tolerability of ruxolitinib, with only limited adverse effects observed and less use of cytostatic drugs previously considered standard therapy for bridging toward HSCT. Although potential treatment bias is a well-known limitation of retrospective studies, these data might endorse a shift towards more targeted anti-inflammatory bridging therapy to HSCT in primary HLH.

Despite these promising clinical data, challenges still remain. It will be of great interest to see the 5-year survival rates of this study to draw a more substantial conclusion. Furthermore, the optimal dosing, treatment duration, and the role of ruxolitinib in the management of primary HLH warrant further investigation. Additionally, its long-term safety profile in the pediatric population requires thorough evaluation.

In conclusion, ruxolitinib holds tremendous potential as a novel therapeutic option for patients with primary HLH. Its targeted approach to modulate cytokine storms represents a new horizon in the treatment landscape of this overwhelming

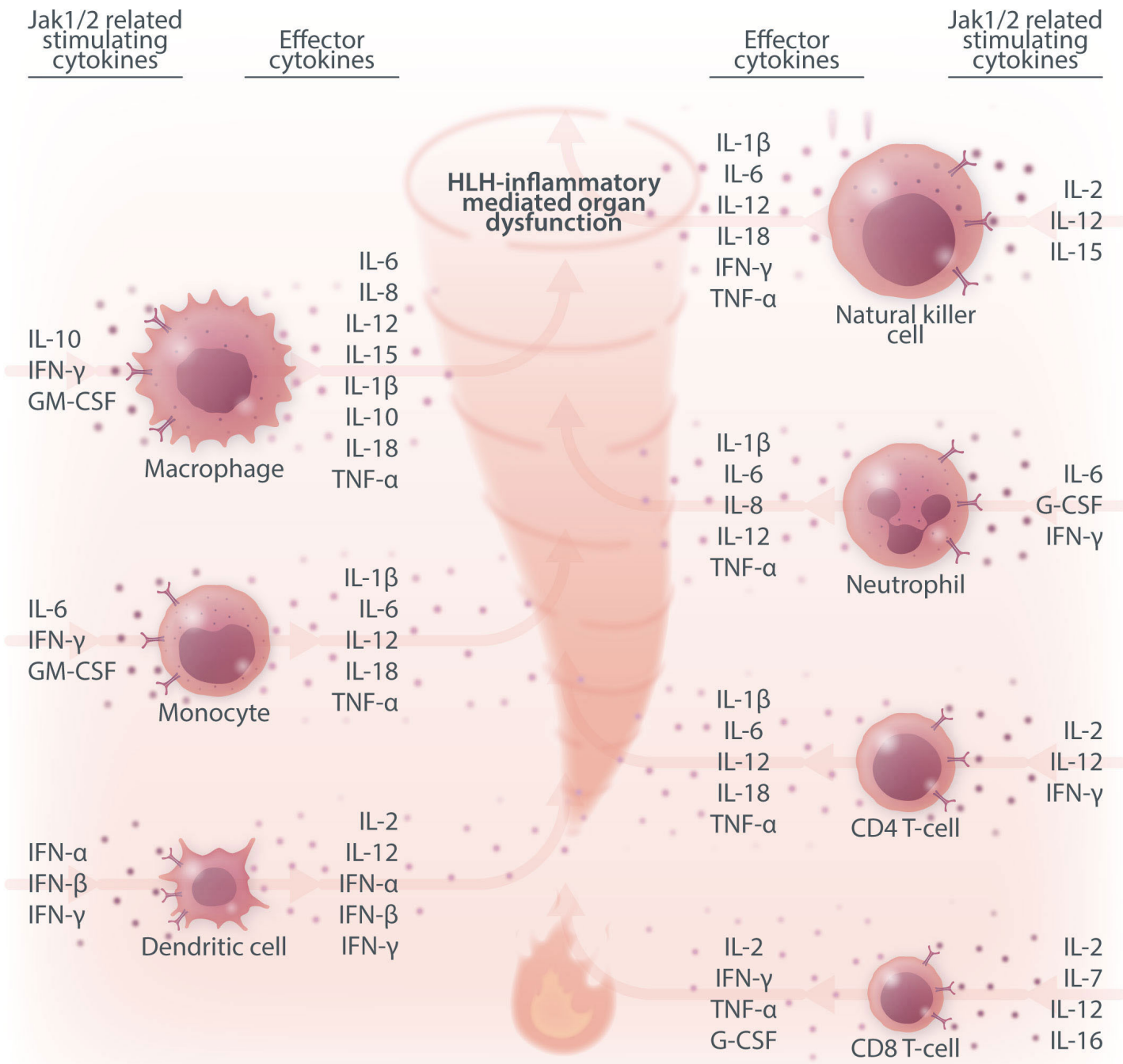

Figure 1. The cytokine-storm and its related cytokines. Activated inflammatory cells release cytokines that are causing a cytokine storm subsequently leading to irreversible tissue damage. Cells active in hemophagocytic lymphohistiocytosis (HLH): activated CD8 and CD4, monocytes, dendritic cells, neutrophils and macrophages. INF: interferon; IL: interleukin; GM-CSF: granulocyte-macrophage colony-stimulating factor; TNF: tumor necrosis factor; NK: natural killer cells.

hyper-inflammatory condition in bridging towards a more definite treatment by HSCT. As we continue to unravel the intricacies of HLH pathogenesis and treatment, further research and clinical trials are essential to substantiate the full potential of JAK inhibition, ultimately improving patient outcomes and quality of life. Future perspectives might include combined cytokine inhibition by adding IFN-γ blockers to JAK inhibitors to synergistically damp the cytokine storm as has been described recently *in vivo*.[7]

Disclosures

No conflicts of interest to disclose.

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