Treatment of hemophagocytic lymphohistiocytosis - today and tomorrow

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Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome with two major forms; primary (familial; FHL) and secondary (acquired) HLH (sHLH). FHL is due to genetic abberations causing defect lymphocyte cytotoxicity, while sHLH in adults commonly is triggered by infections malignancies and autoimmune conditions.

In FHL, functional studies of lymphocyte cytotoxicity are diagnostically valuable, In addition, >90% can get genetic diagnoses. Diagnosis of sHLH is less well defined, and the HLH-2004 diagnostic criteria are recommended but not validated.

Survival in FHL has increased dramatically with around 60% 5-yr survival in HLH-2004. This etoposide/dexamethasone combination is beneficial also in sHLH, including infection-associated HLH, such as severe EBV-HLH, and malignancy-associated HLH (in particular malignancy-triggered HLH). In autoimmune-associated HLH (macrophage activation syndrome, MAS-HLH), etoposide is often a second/third line option.

In severe presumed sHLH we suggest individualized etoposide/corticosteroid-based therapy with 1) etoposide typically once weekly, 2) weekly decisions on etoposide continuation, and 3) lower etoposide dose than in FHL, in particular in adolescents and adults (50-100 mg/m^2 according to age, severity of symptoms, and response to therapy). More intensive therapy, as the full HLH-94/HLH-2004 protocols, may be required in severe EBV-HLH. Biologically, etoposide results in selective deletion of activated T-cells and efficient suppression of inflammatory cytokine production.

Finally, there is still much to learn on sHLH diagnosis and treatment. In the future, we may combine etoposide/corticosteroid with biological treatment (as inhibitors to JAK1/JAK2, IL-1, and/or IFN-gamma) to increase efficacy and reduce side effects. Moreover, the role of SCT in refractory/relapsing sHLH needs to be determined.