Alemtuzumab treatment for hemophagocytic lymphohistiocytosis

Maciej Machaczka, Johan Vaktnäs, Samuel C. C. Chiang and Yenan T. Bryceson

Strout and colleagues present a case of acquired hemophagocytic lymphohistiocytosis (HLH) refractory to typical HLH treatment methods (Alemtuzumab as a bridge to allogeneic SCT in atypical hemophagocytic lymphohistiocytosis. *Nat. Rev. Clin. Oncol.* 7, 415–420).[1] The patient responded well to anti-CD52 monoclonal antibody (alemtuzumab) therapy, which is approved for the treatment of B-cell chronic lymphocytic leukemia (CLL).[2] This approach allowed time for donor search and consequently, successful allogeneic stem-cell transplantation of the patient. On the basis of this case, the authors propose that alemtuzumab is a "rational therapeutic option" in second-line therapy of all HLH types, but advise waiting with the use of alemtuzumab in first-line HLH therapy "until its efficacy has been demonstrated in clinical trials".

The literature on this topic is limited; however, in 2009 Bauer *et al.*[3] reported a case of acquired HLH following alemtuzumab therapy. A 48-year-old woman was treated for T-cell prolymphocytic leukemia with A-CHOP therapy (alemtuzumab, cyclophosphamide, doxorubicin, vincristine and prednisone). After the fourth course of A-CHOP, the patient developed HLH and disseminated tuberculosis. In this case, alemtuzumab might first have induced tuberculosis, and later was responsible for the development of an inflammatory response that resulted in HLH.

Our experience (unpublished) with the use of alemtuzumab and HLH is also different from that presented by Strout and colleagues. We treated a 74-year-old Caucasian male with alemtuzumab monotherapy for relapsed CLL. The diagnosis of CLL was established 12 years earlier, and his CLL treatment, in chronological order, included chlorambucil, fludarabine plus cyclophosphamide, cyclophosphamide plus doxorubicin plus prednisone and alemtuzumab monotherapy (until 3 years before the relapse). 10 years after initial diagnosis, the patient was splenectomized due to idiopathic thrombocytopenic purpura, but remained in complete remission. 2 years later (12 years after initial CLL diagnosis) progressive lymphadenopathy, malaise and sweats indicated a need for renewed CLL treatment. Fluorescent *in situ* hybridization of the bone marrow revealed del 17p (12% of cells), del 11q (40% of cells) and 12+ (30% of cells). *IGHV* status was unmutated. Alemtuzumab monotherapy (injections, 30 mg subcutaneously, three times a week) was initiated resulting in a good clinical response with respect to CLL, but after 2 months of treatment the patient developed fever (40 °C), progressive icterus, edema, ascites, capillary leak syndrome and finally multiorgan failure. An extensive work-up during the time he was treated in the intensive care unit disclosed HLH but did not identify any causative infection. Alemtuzumab was discontinued and HLH therapy, according to the modified HLH-94 protocol with etoposide 150 mg/m^2 intravenously (270 mg total per dose) and corticosteroids,[4] was successfully administered. We speculate that alemtuzumab therapy may aid development of HLH in certain settings by eliminating cytotoxic lymphocytes that usually contribute to the maintenance of immune homeostasis.

Strout and colleagues argue that immunosuppression and effective treatment of the underlying HLH etiology is often sufficient to induce a durable remission in patients with acquired HLH.[1] Although this may be true with respect to infection-associated HLH and autoimmune-associated HLH, patients with malignancy-associated HLH (M-HLH) have a poor outcome despite immunosuppression and treatment of underlying malignancy.[5–7] Moreover, M-HLH often impedes adequate treatment of aggressive malignancy, which results in a poor prognosis. Therefore, guidelines and new effective treatment options for M-HLH in adults are urgently needed. The paper by Strout *et al.*[1] provides an interesting perspective on this issue. However, our patient and the one described by Bauer *et al.*[3] raise important concerns regarding the effectiveness of alemtuzumab in controlling HLH, as alemtuzumab was associated with onset of HLH. Thus, knowledge about HLH should be mandatory among physicians who treat patients with alemtuzumab and, without more experience relating to alemtuzumab and HLH, caution is indicated when using this potent immunosuppressive drug for treatment of HLH.

*Hematology Center Karolinska, M54, Karolinska University Hospital Huddinge, 141 86 Stockholm, Sweden (**M. Machaczka**). Hematology Section, Varberg Hospital, 432 81 Varberg, Sweden (**J. Vaktnäs**). Center for Infectious Medicine, Department of Medicine, Karolinska Institute, Karolinska University Hospital Huddinge, 141 86 Stockholm, Sweden (**S. C. C. Chiang, Y. T. Bryceson**).*

Correspondence to: M. Machaczka
maciej.machaczka@ki.se

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Competing interests
The authors declare no competing interests.

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