be forthcoming in the the randomized phase 3 study evaluating the role of brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone (Echelon-2 trial) vs standard of care in first-line treatment of systemic ALCL.

The study by Pro et al, on the basis of long-term data, demonstrates the pivotal role of brentuximab vedotin as a modality for curing a subset of patients with R/R systemic ALCL.

*Conflict-of-interest disclosure: The author declares no competing financial interests.* ■

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● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Bergsten et al, page 2728

# Etoposide for HLH: the limits of efficacy

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In this issue of *Blood*, Bergsten et al report on the pediatric observational treatment study hemophagocytic lymphohistiocytosis (HLH)-2004 and show that upfront ciclosporin A (CSA) and intrathecal steroids do not further improve the success of the etoposide-based HLH-94 protocol.[1]

HLH is a life-threatening hyperinflammatory syndrome characterized by uncontrolled activation of lymphocytes and macrophages resulting in tissue infiltration and a dramatic cytokine storm. The combination of the clinical and laboratory features that define HLH is the manifestation of a group of hyperinflammatory conditions with variable pathways.[2] The best-defined etiology of HLH is due to mutations in genes regulating lymphocyte cytotoxicity. However, a number of other conditions can be associated with HLH, including rheumatic, malignant, and metabolic diseases or immunodeficiencies. Infections can trigger HLH manifestation in all of these disorders, but infection can also be the only disease-associated factor.[3] HLH can develop at any age.

Without treatment, the prognosis of HLH is dismal.[4] The introduction of etoposide was the first major advance in the treatment of this disease. The etoposide-based treatment protocol HLH-94 consisted of 8 weeks of induction therapy and subsequent continuation therapy until hematopoietic stem cell transplantation (HSCT) for patients with familial, relapsing, or severe and persistent HLH. It resulted in a 5-year survival rate of 54%, a remarkable achievement.[5] Nevertheless, 29% of patients died before HSCT, and 19% displayed late neurological sequelae, calling for additional improvements. HLH-2004 intended to address these problems by starting CSA upfront instead of at week 9 and by recommending HSCT, if indicated, as soon as an appropriate donor was available. Corticosteroids were added to the intrathecal methotrexate therapy.

In a remarkable international effort, the study succeeded in recruiting 369 children from 27 countries. A total of 46% had a proven underlying genetic condition (in 80%, at least a partial genetic analysis was performed). A historical comparison with HLH-94 shows that the overall study results do not provide a rationale for incorporating the introduced protocol changes into standard of care. Although pre-HSCT mortality improved from 27% to 19%, this did not reach significance. Also, the overall 5-year survival rate remained unchanged (62% in HLH-2004 vs 56% in HLH-94). Considering the concomitant improvements in supportive therapies, this does not support a positive effect of upfront CSA. Furthermore, the introduction of intrathecal steroids did not improve the incidence of neurological complications.

In addition, somewhat disappointingly, the goal of more rapid HSCT was not fully achieved; the medium time to HSCT remained >150 days. Among the 75 patients who died before HSCT, one-third died after the first 2 months of treatment, suggesting that more lives can be saved by earlier HSCT. For clinical practice, this means that the search for a stem cell donor should be started immediately in patients with likely primary HLH, based on clinical assessment and rapidly available immunological tests.[6] Finally, the outcome of HSCT was equal to the previous study; 5-year post-HSCT survival was 67% compared with 66% in HLH-94. Although the study recommended busulfan-based myeloablative conditioning, details on the regimes that were actually used were not reported. It is likely that most patients were recruited before the widespread use of reduced-intensity regimes that lead to a better outcome.[7,8] Importantly, the study revealed no additional safety concerns, in particular demonstrating that the risk of developing acute myeloid leukemia after etoposide therapy (observed in 1 patient in this study) is clearly lower than the risks of severe HLH.

One of the questions that is discussed by the authors is whether treatment intensity is maintained long enough. Less therapy reduction is proposed for familial/genetic HLH (FHL) patients beyond week 6. However, data supporting this proposal are limited: 6 out of 8 patients (4 with confirmed FHL) who died on days 43 to 59 had refractory or reactivated HLH. It is not clear how many of them achieved an initial full remission and if they had deviations from the etoposide dosing scheme, which were allowed in the protocol. Of note, HLH-2004, like HLH-94, was a pediatric study. Also, patients with underlying diseases were excluded. This is relevant because etoposide-based therapy is widely used for the treatment of HLH in older patients and patients with underlying diseases, who would not have been eligible for the HLH-94 study. Although rapid treatment with etoposide can be lifesaving in these patient groups as well, not all patients fulfilling the HLH-2004 diagnostic criteria require etoposide. Moreover, in some cases, modification of dosing and treatment duration may be appropriate. In support of this, a subgroup analysis in HLH-2004 indicated that some of the deaths within the first 2 months of treatment, occurring predominantly in patients without familial disease, may have been treatment related. This group of patients with secondary HLH can be much better defined due to the more extensive genetic analysis in the HLH-2004 study. Future analysis of the study data should use the opportunity to provide more information on this patient subgroup.

Importantly, exciting new therapeutic options that are more precisely targeted to the immunological disease pathophysiology are currently being tested in pilot studies, including alemtuzumab, tocilizumab, the JAK1/2 inhibitor ruxolitinib, and an anti–interferon-γ monoclonal antibody. The initial results from these studies are promising, but given the many different etiologies of HLH, the role of these new options in therapy will require careful study. In particular, from a world-wide perspective, it is likely that etoposide-based protocols will remain in use for a number of years to come. Therefore, the HLH steering committee of the Histiocyte Society is currently issuing recommendations on the use of etoposide-based therapy in different HLH contexts based on >20 years of experience with etoposide. Whether the new treatments result in outcome differences of a size that allows for a sufficiently powered randomized trial in such a rare disease remains to be seen. In any case, international collaboration, as exemplified in HLH-94 and HLH-2004, will be a crucial basis for further progress in the treatment of patients with this severe condition.

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● ● ● MYELOID NEOPLASIA

Comment on Zhao et al, page 2762

# Single-cell dissection of monosomy 7 syndromes

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In this issue of *Blood*, Zhao et al perform single-cell RNA sequencing (scRNA-seq) of bone marrow–derived CD34$^+$ cells from patients with monosomy 7. Identifying cells with chromosome 7 aberrations, they uncover reduced transcription of genes upholding genomic integrity and concomitant accumulation of somatic mutations.[1]

In 1960, Nowell and Hungerford[2] discovered a small chromosome in the white blood cells of patients with chronic myelogenous leukemia (CML), signifying the first chromosomal abnormality associated with cancer. Cytogenetic analyses have since revealed that chromosomal abnormalities are a common feature of many cancers, with distinct aberrations being associated with specific forms of cancer. Myeloid malignancies encompass a heterogeneous group of clonal hematopoietic stem- and progenitor-cell (HSPC) disorders.[3] In addition to CML, they include myeloproliferative neoplasms (MPNs), myelodysplastic syndrome (MDS), and acute myeloid leukemia (AML). Acquired HSPC chromosomal abnormalities are 1 of the main risk factors for developing myeloid malignancies, characterized by impaired hematopoiesis and cytopenias. The incidence of myeloid malignancies increases with age. In the elderly, del(5q) represents the most common chromosomal aberration, followed by the complete or partial loss of chromosome 7, termed monosomy 7 (−7). In children, approximately 20% of leukemias are of myeloid origin, with −7 representing a common chromosomal aberration. Importantly, −7 is associated with refractory cytopenias and a high risk of progression to AML.[4] Dissecting how abnormalities affecting large chromosomal regions mechanistically give rise to distinct cancers is challenging. Because chromosomal composition varies among species, animal models are not useful.

Human genetics have provided insights into −7. Inherited bone marrow failure syndromes caused by mutations in genes required for DNA repair, chromosomal stability, and telomere elongation are associated with an increased risk of acquiring somatic mutations that often manifest as