inside blood commentary

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Pro et al, page 2709

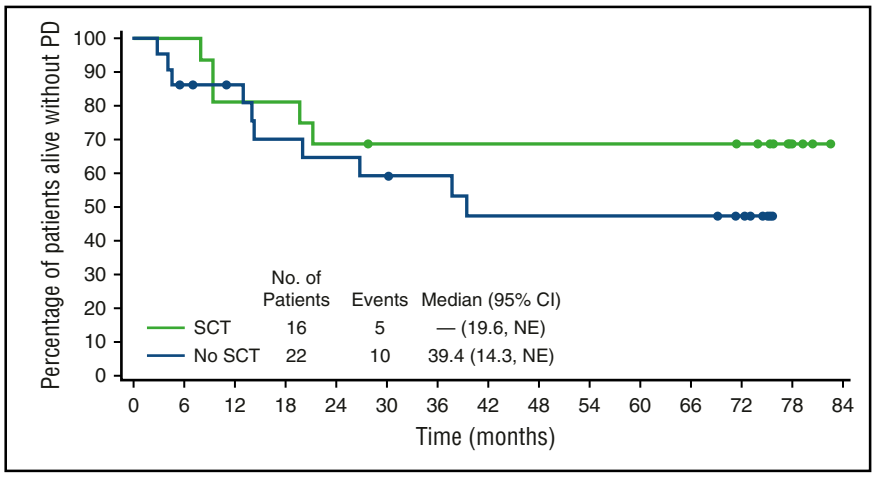
ALCL: is it now a curable disease?

Pier Luigi Zinzani UNIVERSITY OF BOLOGNA

In this issue of *Blood*, Pro et al have reported that it is possible to cure a subset of patients with relapsed or refractory (R/R) systemic anaplastic large cell lymphoma (ALCL) with brentuximab vedotin.[1]

The 5-year update of brentuximab vedotin treatment in patients with R/R systemic ALCL demonstrates durable remission with real potential for a cure. Among the 38 patients who obtained a complete response (CR), the median progression-free survival (PFS) had not been reached and at 5 years was 57%.

Approximately 40% to 65% of patients with systemic ALCL develop recurrent disease after first-line therapy.[2] At relapse, the disease has historically been resistant to conventional multiagent chemotherapy regimens, and there is no established standard of care. High-dose therapy and autologous stem cell transplantation (SCT) may result in long-term remission in 30% to 40% of patients, but the benefit of autologous SCT is limited to patients with chemotherapy-sensitive disease.[3] Even more concerning are patients with primary chemotherapy-refractory disease for whom long-term survival rarely exceeds 15% to 17%.[2] Disease recurrence still remains the principal cause of autologous SCT failure, and early disease progression after transplant (ie, within 6 months from high-dose conditioning) is the most important predictor of unfavorable outcome. No standard treatment options exist for patients with disease relapse after autologous SCT or for patients not eligible for autologous SCT, a common issue resulting from unsatisfactory pretransplant cytoreduction and/or the substantial risk of morbidity due to toxicity from previous therapies.



PFS by SCT status. End-of-study PFS in patients with a best response of CR subset by receipt of consolidative SCT. See Figure 3B in the article by Pro et al that begins on page 2709.

Brentuximab vedotin, an antibody-drug conjugate targeting CD30, may represent the best candidate among the newly developed agents for the treatment of R/R systemic ALCL.[4] In fact, systemic ALCL is characterized by the expression of CD30. The favorable activity of this agent in R/R systemic ALCL was clearly documented by Pro et al[5] in a phase 2 study involving 58 patients: 86% obtained a response, which was a CR in 57% with a median PFS of 13.3 months. This high response rate was seen in pretreated patients who previously had a poor prognosis and in primary R/R patients. In addition, there was no differences in terms of CR rate between anaplastic lymphoma kinase–negative (ALK^-) and ALK^+ patients. The same relevant proportion of CR in this subset of patients also emerges from the brentuximab vedotin named patient program experiences across Europe.[6-9]

Recently, a retrospective large multicenter Italian study of 40 patients with R/R systemic ALCL treated with brentuximab vedotin outside clinical trials shows results similar to those in the pivotal phase 2 study and represents the largest group ever reported in a real-world context.[5,10] In the Pro et al 5-year update study, PFS was improved in CR patients who received a consolidative transplant compared with patients without transplant (69% vs 48%) (see figure). These specific data suggest that it is possible to obtain long-term disease control without transplant consolidation and have a real chance of curing a subset of patients with R/R systemic ALCL with brentuximab vedotin only.

Finally, the lengthy follow-up data definitively confirm that patients with systemic ALCL who were treated with brentuximab vedotin have obtained a real long-term clinical benefit. The climax of this story may

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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Comment on Bergsten et al, page 2728

Etoposide for HLH: the limits of efficacy

Stephan Ehl UNIVERSITY OF FREIBURG

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.