The estimated average tumor purity in this study was 75%, which, although low by modern leukemia and lymphoma sequencing standards, is an improvement in signal-to-noise ratio for Hodgkin lymphoma given the incredible rarity of the Reed-Sternberg cell in its background nest of inflammatory infiltrate. Previous studies relying on laser capture microdissection could also increase the signal-to-noise ratio, but at the cost of time, effort, and still-low cell numbers.

This work raises additional questions. Variant allele frequencies range from 2% to 100% within single cases. Does this imply intratumoral heterogeneity? Do individual or multiple HRS cells exist as clones and subclones with different alterations and characteristics within the same lymphoma, and if so, what would that mean for molecularly targeted therapy?

Overall, this work is exciting for several reasons. It advances our knowledge of the genetic makeup of cHL but also demonstrates the feasibility of a new technique that could in the future be extended to provide additional information about transcription and potentially protein expression. The demonstration that restoration of B2M loss can reverse a characteristic phenotype is an important functional validation of a key finding and is timely and relevant because immune therapies are now being explored in Hodgkin lymphoma.10

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

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The problem of acquired hemophilia

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In this issue of Blood, Andreas Tiede et al report the results of a German, Austrian, and Swiss registry (GTH-AH study) of acquired hemophilia and identify prognostic factors that may guide the choice of immunosuppressive treatment (IST) to eradicate the autoantibody contributing to the outcome of the syndrome.1

Acquired hemophilia A (AHA) is an autoimmune disease caused by an inhibitory autoantibody to factor VIII (FVIII) with an incidence of approximately 1.48/million per year.2 The syndrome is primitive in ~50% of the patients or associated with a variety of clinical conditions (autoimmune disorders, solid tumors, lymphoproliferative diseases, and pregnancy).3 The therapeutic aim is twofold: control of bleeding (of variable intensity at presentation) and eradication of the antibody by the choice of IST.4

The GTH-AH registry is a multicenter, prospective, observational study in which a uniform immunosuppressive regimen was applied in 102 consecutive patients. The primary end point was the time to achieve partial remission (PR) defined as FVIII $>50$ IU/dL and no active bleeding after stopping any hemostatic drug for $>24$ hours. Secondary end points were time to complete remission (CR) defined as PR plus a negative inhibitor test result, overall survival, adverse events (AEs), and cause of death.

IST was prednisolone alone in weeks 1 to 3. If PR was not achieved, cyclophosphamide was added in weeks 4 to 6 and rituximab with prednisolone starting in week 7.

The primary end point was achieved by 83% of patients after a median of 31 days, mainly in those with FVIII $\geq$1 IU/dL (89%) and within a shorter time (24 days). PR with steroids alone in $<21$ days was more common in patients with FVIII $\geq$1 IU/dL and inhibitor level $<20$ Bethesda units (BU)/mL ($P < .0001$). Thirty percent of the AEs occurred in relation to the IST, including infections that are the leading cause of death. A high rate of infections and related mortality has been confirmed in the available studies (11%, 4%, and 12% of patients in a United Kingdom surveillance study2 and in the EACH2 and SACHA1 registries, respectively), whereas death due to bleeding, compared with historical data, substantially decreased in the last few years (from 22% to 2.9%).

Published treatment guidelines recommend IST as soon as the diagnosis is made, because the patients remain at risk of severe and fatal hemorrhage until the inhibitor has been eradicated.7 Immunosuppressive drugs usually administered are steroids alone or steroids plus cytotoxic agents (cyclophosphamide), although there is increasing use of rituximab either alone or in combination with other agents.

Therefore, identifications of prognostic factors on which to tailor the type of IST may be important, because for their characteristics (high median age and concomitant diseases as malignancy, autoimmune disorders, diabetes, and renal or vascular diseases), the patients are at high risk of AEs.

Available data in relation to the present status of prognostic factors are at variance.
Predicting a positive response are low inhibitor level and a short interval between the appearance of the inhibitor and the start of therapy.\textsuperscript{3} FVIII level and inhibitor titer at diagnosis are not significantly associated with outcome.\textsuperscript{2} The likelihood of achieving CR was influenced by the presenting inhibitor titer and FVIII level.\textsuperscript{5}

The IST regimens are also variable in both the dosage and type of agents and with different outcome. There is no difference in inhibitor eradication or mortality between patients treated with steroids alone and combined therapy,\textsuperscript{2,6} and stable CR is more likely with steroids and cyclophosphamide than with steroids alone.\textsuperscript{5}

Different regimens have various incidences of AEs, but a higher proportion of patients treated with steroids and cyclophosphamide experienced AEs compared with steroids alone.\textsuperscript{3} The use of steroids, especially in relation to dosage and time of administration, could be revised in a population at high risk of AEs.

In the GTH study, FVIII ≥1 IU/dL and inhibitor level <20 BU/mL were independent predictors of overall survival and can define a subgroup of patients with better prognosis; this subgroup comprised about one-third of patients who may benefit from less aggressive treatment with a lower rate of AEs.

Future randomized studies are unlikely because of the rarity of the disease and the difficulty in collecting patients. This study is not a randomized study; nevertheless, it has been carried out with uniformity and therefore gives valuable information that can be followed in clinical practice.

Considering the high frequency of AEs, the future problem could be to identify the population of patients requiring less intensive therapy and how to carry out that therapy.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Comment on Kim et al, page 1107

Engineering regulatory T cells against factor VIII inhibitors

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In this issue of \textit{Blood}, Kim et al show that engineered factor VIII (FVIII)-specific regulatory T cells inhibit immune responses to FVIII\textsuperscript{1}, suggesting the possibility of cellular therapy for FVIII inhibitors in hemophilia A.

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\begin{center}
 \textbf{Interactions between engineered Tregs and effector T cells (Teffs).} A gene construct encoding for a T-cell receptor (TCR) specific for FVIII peptide is transduced into polyclonal Tregs, producing Tregs expressing that TCR. Tregs interact with antigen-presenting cells (APCs) via human major histocompatibility complex II (MHCII), as do Teffs. Tregs exert suppressive effects on Teffs, preventing immune responses to antigen and promoting tolerance. Kim et al demonstrate in vitro that such engineered Tregs can suppress the typically polyclonal responses to whole FVIII, despite expressing TCRs specific for a single small FVIII peptide. Could this result in the off-target suppression of T-cell responses to non-FVIII antigens, such as antigens from pathogens or vaccines?
\end{center}
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