that this specific variant increases the expression of GATA3. GATA3 plays a major role in T-cell development and is specifically essential for type 2 innate lymphoid cells, key regulators of host immune response to parasitic infections and allergic inflammation. Interestingly, these cells express high levels of CRLF2 and activated JAK-STAT signaling.[9] Thus, there may be a causal relationship between an inherited allele variant that increases the expression of GATA3 and an increased specific risk for CRLF2 expressing ALL in children with and without DS.

Although biologically fascinating, the identification of children at higher risk of developing ALL is currently of no clinical consequence. Theoretically, it may be possible to identify such children. Examples could be children with a combination of these genetic variants or children with genomic evidence of a preleukemic clones. However, what could be done with such information? Prevention of childhood leukemia is therefore a major scientific and clinical challenge. Some progress has been recently made in mouse models through modulating the microbial microenvironment.[10] The genomic tools for identification of at-risk patients are already here. All that remains is to learn to alleviate bad luck.

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REFERENCES

1. Brown AL, de Smith AJ, Gant VU, et al. Inherited genetic susceptibility of acute lymphoblastic leukemia in Down syndrome. *Blood*. 2019;134(15):1227-1237.
2. Tomasetti C, Vogelstein B. Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science*. 2015;347(6217):78-81.
3. Schäfer D, Olsen M, Lähnemann D, et al. Five percent of healthy newborns have an *ETV6-RUNX1* fusion as revealed by DNA-based GIPFEL screening. *Blood*. 2018;131(7):821-826.
4. Greaves M. A causal mechanism for childhood acute lymphoblastic leukaemia [published correction appears in Nat Rev Cancer. 2018;18(8):526]. *Nat Rev Cancer*. 2018;18(8):471-484.
5. Vijayakrishnan J, Studd J, Broderick P, et al; PRACTICAL Consortium. Genome-wide association study identifies susceptibility loci for B-cell childhood acute lymphoblastic leukemia [published correction appears in Nat Commun. 2019;10(1):419]. *Nat Commun*. 2018;9(1):1340.
6. Izraeli S. The acute lymphoblastic leukemia of Down syndrome–genetics and pathogenesis. *Eur J Med Genet*. 2016;59(3):158-161.
7. Gocho Y, Yang JJ. Genetic defects in hematopoietic transcription factors and predisposition to acute lymphoblastic leukemia. *Blood*. 2019;134(10):793-797.
8. Perez-Andreu V, Roberts KG, Harvey RC, et al. Inherited GATA3 variants are associated with Ph-like childhood acute lymphoblastic leukemia and risk of relapse. *Nat Genet*. 2013;45(12):1494-1498.
9. Mjösberg J, Bernink J, Golebski K, et al. The transcription factor GATA3 is essential for the function of human type 2 innate lymphoid cells. *Immunity*. 2012;37(4):649-659.
10. Martín-Lorenzo A, Hauer J, Vicente-Dueñas C, et al. Infection exposure is a causal factor in B-cell precursor acute lymphoblastic leukemia as a result of Pax5-inherited susceptibility. *Cancer Discov*. 2015;5(12):1328-1343.

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Comment on Stephens et al, page 1238

PET-adapted treatment of Hodgkin lymphoma

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The long-term follow-up analysis of the SWOG0816 trial, presented by Stephens et al[1] in this issue of *Blood*, reminds us that long-term retrospect is needed to understand studies of a highly curable disease of the young.

Advanced-stage Hodgkin lymphoma (aHL) is most commonly treated with adriamycin, bleomycin, vinblastine, and doxorubicin (ABVD) or less commonly with a more intensive regimen containing bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPPesc). ABVD is well tolerated, but results in ~30% treatment failure. BEACOPPesc is more effective but too toxic to be given to all patients. Many observational studies have shown that early interim positron emission tomography (PET) is highly prognostic in aHL.[2] This led to several trials investigating early PET response–adapted therapy, aiming to improve outcomes and reduce the overall toxicity burden.

The United Kingdom–led RATHL study included 1214 aHL patients.[3] The 84% of patients with a negative PET after 2 ABVD cycles (PET2) were randomized to ABVD or adriamycin, vinblastine, and doxorubicin (AVD) for the remaining 4 cycles. There was no efficacy difference between the ABVD and AVD arms (so no need to give bleomycin beyond 2 cycles of ABVD in PET2-negative patients), and 3-year progression-free survival (PFS) for all PET2-negative patients was 86%. In the Italian GITIL0607 study, 81% of 782 enrolled patients with aHL were PET2 negative, and they reached a similar 3-year PFS of 87% with continued ABVD treatment.[4] With 2 larger and relatively recent studies for comparison, the outcomes for PET2-negative patients in the SWOG0816 study are disappointing. Of 336 patients, 82% were PET negative after 2 cycles of ABVD. Like in the RATHL and GITIL0607 studies, they continued to a total of 6 cycles of ABVD, but the article by Stephens et al reports a 5-year PFS of only 74% for those PET2-negative patients. There is a long way from 86% and 87% to 74%, so what is the reason for this difference? Somehow, the negative predictive value of the central PET review of the SWOG study was lower than in the other studies. However, the longer follow-up in the SWOG study is also an important factor, because the article reports 5-year PFS with a median follow-up of 5.9 years compared with the 2 previous studies, which reported 3-year PFS, both with median follow-up of just over 3 years. As witnessed by the PFS curves presented by Stephens et al, relapses and other PFS events do occur beyond 2 to 3 years, apparently relatively more frequently than in the patients with insufficient initial response to chemotherapy.

Like in the RATHL and GITIL0607 studies, PET2-positive patients in the SWOG0816 study were offered treatment intensification with BEACOPPesc. Among the 18% of PET2-positive patients in the SWOG0816

study, 5-year PFS was 66%. This is in line with the 68% 3-year PFS and the 60% 3-year PFS observed in the RATHL and GITIL0607 studies and compares very favorably with the observational studies in which PET2-positive patients continued treatment with ABVD and reached long-term PFS rates of 10% to 35%. The catch is an alarmingly high rate of secondary cancers among the patients treated with BEACOPPesc. Seven of those patients (14%) experienced second malignancies within the 5.9 years of median follow-up; even though the numbers are small, this is even higher than in the long-term analyses of the German studies in which patients received 6 or 8 cycles of BEACOPPesc.[5] Interestingly, in the RATHL study in which PET2-positive patients received only 4 cycles of BEACOPPesc,[3] the cumulative rate of second malignancies at 3.4 years of follow-up was 1.7%. In the GITIL0607 study, in which PET2-positive patients received 4 cycles of BEACOPPesc, followed by 4 cycles of BEACOPPbaseline (same drugs and schedule as BEACOPPesc, but lower dose-intensity), no second cancers had been reported at 3.6 years median follow-up.[4]

What lessons can we learn from the 5-year update of the SWOG0816 study?

1. It is an important reminder that relapses and second cancers occur late in aHL patients; therefore, long-term follow-up reports like the one presented by Stephens et al are crucial to fully interpret study results.
2. Early PET response–adapted ABVD-based therapy for aHL results in improved outcomes for early interim PET-positive patients and in excellent overall outcomes (94% 5-year overall survival in SWOG0816; 97% 3-year overall survival in RATHL and GITIL0607).
3. Interim PET is far from perfect, and the study by Stephens et al suggests an even higher rate of false-negative results than other studies; therefore, more sensitive tools to detect residual unresponsive disease are needed.
4. Six cycles of BEACOPPesc following 2 cycles of ABVD lead to an unacceptable risk for second malignancies and do not offer better disease control than 4 cycles of BEACOPPesc, as given in the RATHL study.

The introduction of PET and PET response–adapted treatment were the most important new developments in the management of aHL 10 to 15 years ago. Since then, effective targeted agents (brentuximab vedotin, checkpoint inhibitors) have been introduced, and the Echelon-1 study showed improved efficacy in first-line treatment of aHL when bleomycin is replaced by brentuximab vedotin (ABVD vs AVD-A [adriamycin, vinblastine, dacarbazine, brentuximab vedotin]).[6] Interestingly, 3-year PFS for ABVD-treated patients in the standard arm of the Echelon-1 study was 76%, regardless of PET2 results, which is better than the 5-year PFS for PET2-negative patients in the SWOG0816 study.[7] Recently, refined and very sensitive tools to assess treatment response and minimal residual disease using serum markers and circulating tumor DNA analyses have been reported.[8,9]

The ongoing COBRA study from the European Organisation for Research and Treatment of Cancer is an attempt to combine novel regimens and refined response adaptation in aHL[10]: all patients receive 1 cycle of AVD-A, after which PET/computed tomography is performed, along with analyses of circulating tumor DNA and disease-specific serum chemokines. Responding patients continue treatment with AVD-A, whereas nonresponders are offered intensification using the experimental brentuximab vedotin, etoposide, cyclophosphamide, adriamycin, dacarbazine, and dexamethasone regimen, which is undergoing randomized comparison with BEACOPPesc in the ongoing German HD21 trial.

It is hoped that more effective less toxic regimens, as well as better tools for response-adapted treatment, will further improve the efficacy and safety of first-line treatment of aHL.

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REFERENCES

1. Stephens DM, Li H, Schöder H, et al. Five-year follow-up of SWOG S0816: limitations and values of a PET-adapted approach with stage III/IV Hodgkin lymphoma. *Blood*. 2019; 134(15):1238-1246.
2. Hutchings M, Loft A, Hansen M, et al. Position emission tomography with or without computed tomography in the primary staging of Hodgkin's lymphoma. *Haematologica*. 2006; 91(4):482-489.
3. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med*. 2016;374(25):2419-2429.
4. Gallamini A, Tarella C, Viviani S, et al. Early chemotherapy intensification with escalated BEACOPP in patients with advanced-stage Hodgkin lymphoma with a positive interim positron emission tomography/computed tomography scan after two ABVD cycles: long-term results of the GITIL/FIL HD 0607 Trial. *J Clin Oncol*. 2018;36(5):454-462.
5. Borchmann P, Goergen H, Kobe C, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *Lancet*. 2018;390(10114): 2790-2802.
6. Connors JM, Jurczak W, Straus DJ, et al; ECHELON-1 Study Group. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med*. 2018; 378(4):331-344.
7. Straus DJ, Długosz-Danecka M, Alekseev S, et al Brentuximab vedotin with chemotherapy for stage 3/4 classical Hodgkin lymphoma: Three-year update of the ECHELON-1 study. Presented at the 2019 American Society of Clinical Oncology Annual Meeting. 3 June 2019. Chicago, IL.
8. Spina V, Bruscaggin A, Cuccaro A, et al. Circulating tumor DNA reveals genetics, clonal evolution, and residual disease in classical Hodgkin lymphoma. *Blood*. 2018; 131(22):2413-2425.
9. Plattel WJ, Alsada ZN, van Imhoff GW, Diepstra A, van den Berg A, Visser L. Biomarkers for evaluation of treatment response in classical Hodgkin lymphoma: comparison of sGalectin-1, sCD163 and sCD30 with TARC. *Br J Haematol*. 2016; 175(5):868-875.
10. ClinicalTrials.gov. Very early PET-response adapted targeted therapy for advanced Hodgkin lymphoma: a single-arm phase II study (COBRA). Identifier: NCT03517137. https://clinicaltrials.gov/ct2/show/NCT03517137?term=Hutchings&cond=Hodgkin&rank=1. Accessed 26 August 2019.

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