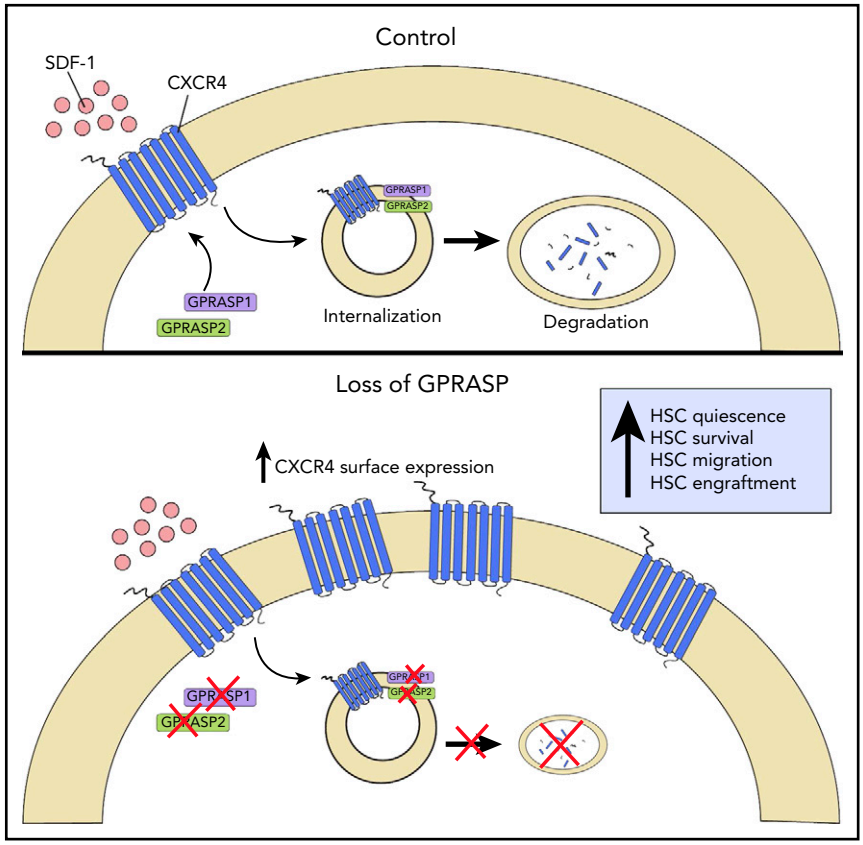

Schematic representation of GPRASP control of CXCR4-mediated HSC functions. In homeostasis (Control), GPRASP1 and GPRASP2 regulate CXCR endocytic trafficking and degradation. In the absence of GPRASP1 or GPRASP2, CXCR4 accumulates in HSCs, promoting HSC quiescence, survival, migration, and engraftment capacity. Illustration by Christina M. Termini, UCLA.

The results also raise exciting fundamental questions and possibilities regarding the broader role of GPRASP proteins in regulating other GPCRs expressed by HSCs.[10] At the same time, GPRASP1 and GPRASP2 represent attractive new molecular targets for pharmacologic or biologic interventions to enhance human HSC engraftment and mobilization in patients.

Conflict-of-interest disclosure: J.P.C. declares no competing financial interests. ■

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LYMPHOID NEOPLASIA

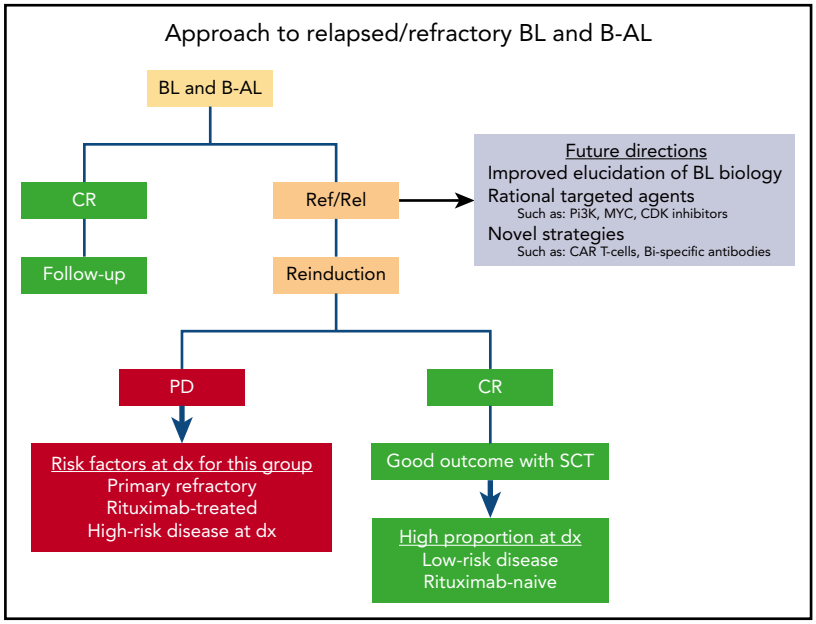
Comment on Woessmann et al, page 1124

Tackling Burkitt when it's back

Aron Simkins and Kieron Dunleavy | George Washington University Cancer Center

In this issue of *Blood*, Woessmann et al report on outcomes of 157 children with refractory or relapsed Burkitt lymphoma (BL) or Burkitt leukemia (B-AL) who were included in non-Hodgkin lymphoma-Berlin-Frankfurt-Münster (NHL-BFM) studies over a 30-year period.[1] Despite various aggressive strategies, survival in the group that did not achieve remission with primary therapy remains distressingly low.

BL is a highly aggressive disease and the most common type of NHL in children. It is characterized by a very high proliferation rate and deregulation of the *MYC* gene. It consists of endemic, sporadic, and immunodeficiency-associated variants. Although it represents less than 5% of NHL cases in adults overall, it has a much higher incidence in the adolescent and young adult (AYA) population.[2,3] The outcome for pediatric and AYA patients with the disease is excellent. With current standard treatment approaches that were modeled on 2 large cooperative group trials,[4,5] pediatric and AYA patients have an event-free survival (EFS) and overall



Schematic representation of an approach to treating pediatric patients with relapsed or refractory BL. CAR, chimeric antigen receptor; CR, complete remission; dx, diagnosis; PD, progressive disease; Ref, refractory; Rel, relapsed; SCT, stem cell transplantation.

survival (OS) rate above 90% for patients with early-stage disease and an OS rate above 80% for those with advanced-stage disease. Recently, an international randomized phase 3 study investigated whether adding rituximab to standard therapy was beneficial for patients with high-risk disease; an interim analysis showed a 1-year EFS advantage was 94% in the group that received rituximab, and 81% in the group that received standard therapy alone.[6] This led to early cessation of the randomization and to the conclusion that all pediatric patients with BL should receive rituximab. Given the very good outcomes in pediatric patients, attempts are currently underway to develop less toxic approaches with excellent outcomes equivalent to those in current standard approaches.[7] However, patients with relapsed or refractory disease still have dismal outcomes, and there is no standard treatment approach for managing their disease.

The Woessmann et al study assesses characteristics, treatment paradigms, and outcomes of patients with BL or B-AL who had refractory or relapsed disease in a large cohort of 1979 patients treated on NHL-BFM studies over a 30-year period. In all, 157 patients (7.9%) had refractory or relapsed disease after first-line therapy and at a follow-up of 5 years; the probability of survival was disappointingly just 18.5%. More than one third of patients progressed during initial therapy, and overall, progressions and relapses occurred early at a median of 0.4 years after the start of treatment. In assessing the risk factors for survival in this relapsed or refractory group, progression during initial therapy was associated with a particularly poor outcome (11% survival). Because the study spanned 3 decades, many of the more recently accrued patients received rituximab, and of those who relapsed, just 10% survived, which demonstrates that relapses after improved first-line therapy are much more challenging to treat (see figure). Initial high-risk disease was also a poor prognostic factor and, as expected, outcomes were best for patients who had a complete response to reinduction therapy and went on to have a stem cell transplantation (with 63% survival).

Undoubtedly, treating patients who have refractory or relapsed disease after initial therapy for BL or B-AL is a substantial challenge in need of attention, as evidenced by the low survival rate in the Woessmann et al study and others. The difficulties in treating this group of patients is the aggressiveness of the disease when it relapses and how rapidly it progresses. Relapsed or refractory BL/B-AL is also rare, which makes it challenging to conduct clinical trials. Future research needs to better elucidate the biology of the disease and continue to identify molecular aberrations other than *MYC* that are key in BL pathogenesis.[8] Ideally, this will pave the way for testing novel agents in relapsed or refractory patients as well as at diagnosis in those with high-risk features.[9] From our understanding of BL biology, inhibition of targets such as PI3 kinase, cyclin-dependent kinases, and *MYC* is a rational strategy that should be considered for future development.[10] Approaches such as chimeric antigen receptor T-cell therapy and bispecific antibodies, which are effective in acute lymphoblastic leukemia and diffuse large B-cell lymphoma, should also be considered. Given the survival rate of only 18.5% in this relapsed or refractory BL/B-AL pediatric population, there is an urgent need to develop successful novel strategies that use international collaborations between pediatric and adult groups.

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

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RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on van Zeventer et al, page 1161

Does clonal hematopoiesis explain unexplained anemia?

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In this issue of *Blood*, van Zeventer and her colleagues in The Netherlands report mutational profiling in 676 anemic patients ≥60 years old and a group of age-matched nonanemic controls.[1] These study subjects were selected from the LifeLines population cohort, which includes 22 108 people in that age band, most in the northern provinces of The Netherlands. The prevalence of anemia in the LifeLines cohort, just >3%, is considerably lower than in the US National Health and Nutrition Examination Survey (NHANES) III cohort, which may relate to better population health in The Netherlands compared with the United States or germline genetic differences.

Many older people are anemic, and it is not always clear why. In the third US NHANES III cohort, for example, >10% of community-dwelling Americans >60 years of age were found to be anemic when using World Health Organization (WHO) hemoglobin cutoffs to define anemia, including >20% of the oldest old (ie, those over age 85).[2] About 2 out of every 3 NHANES anemia cases were due to nutritional deficiency, renal failure, or inflammation. The other one-third was considered "unexplained."

In the 15 years since the NHANES anemia prevalence data were reported, investigators have proposed various hypotheses to explain unexplained anemia in the elderly as well other "idiopathic cytopenias of undetermined significance" (ICUS).[3] These hypotheses include occult immune-mediated marrow suppression or premature blood cell destruction, stem cell "exhaustion," or undiagnosed myelodysplastic syndromes (MDS).

Definitive diagnosis of immune-mediated cytopenias remains difficult (eg, immune thrombocytopenic purpura remains a diagnosis of exclusion), whereas hematopoietic cell exhaustion is a multifaceted and rather ill-defined phenotype. However, there is certainly suggestive evidence that MDS is underdiagnosed. In 1 Israeli hospital, for example, geriatric patients who were admitted to a ward for patients with cognitive impairment and who were noted to have minor blood count abnormalities underwent in-depth evaluation; 15% ultimately were proved to have MDS.[4] Many elderly patients who might have MDS do not undergo full evaluation of mild cytopenias, especially very old patients with chronic health problems who are living in long-term care facilities in whom MDS, if diagnosed, would not be aggressively treated.

The high prevalence of anemia in the elderly is being reconsidered now that we know that somatic mutations are acquired in all tissues throughout the human lifespan, and that stable expanded blood cell populations derived from hematopoietic stem cells bearing acquired mutations that are associated with hematological neoplasia are present in almost everyone by middle age.[5,6] Most people with somatic mutations and clonal hematopoiesis have normal complete blood counts, however.[7] This remains true even when the mutations are in genes associated with MDS or other myeloid neoplasms and are present at a variant allele frequency (VAF) ≥2%, which is near the detection or reporting threshold of common clinical next-generation sequencing assays and was used to define clonal hematopoiesis of indeterminate potential (CHIP).[8]

In the Dutch series, somatic mutations in blood cells at ≥1% were more frequent in anemic individuals (46.6%) than in controls (39.1%), which is also higher than the prevalence of CHIP in previous series. The relatively small difference in prevalence between anemic people and controls, however, suggests that the mutations do not account for the majority of anemias in elderly people, which is underscored by the fact that there was no difference between groups in the prevalence of the 3 most common CHIP mutations: *DNMT3A*, *TET2*, and *ASXL1*. Instead, other genes were more commonly mutated in anemic persons, including *SF3B1*, strongly associated with ring sideroblasts and ineffective erythropoiesis, and the dreaded *TP53*.

With follow-up, most clonal populations were stable over time and exhibited little change in VAF, at least during the length of the monitoring period. It is an unresolved question why this stability occurs so commonly. Mutations such as DNMT3A R882H give hematopoietic cells a growth advantage compared with wild-type cells, yet clonal sweeping with complete dominance of hematopoiesis is uncommon in the absence of secondary mutations, for unclear reasons.

Interestingly, given the relationship between CHIP and inflammation,[9] mutations were more commonly detected in people thought to have anemia of inflammation compared with other anemia types, such as nutritional anemia. "Inflammation" is somewhat of a loosey-goosey concept, as there are many different inflammatory pathways and biomarkers. In the Dutch series, inflammation was defined by either elevated high-sensitivity C-reactive protein, unexplained leukocytosis, or an iron pattern consistent with inflammatory changes.

The Netherlands is the nation with the tallest people on the planet, and this new series underscores that size matters, at least when it comes to hematopoietic clones.