critical for preventing AMD. Such a view is probably too simplistic as the relative roles of CFH and CFHR-1 in vivo are likely to be determined also by their plasma concentrations, relative affinity for C3b/C3d and host cell surface, and respective potency as a direct or indirect C5 convertase inhibitor. Additionally, CFHR-1/CFHR-3 deficiency is often associated with CFH autoantibodies, which may significantly impact aHUS and AMD risks as well.

Whether or not the findings of Heinen et al can readily explain the observed correlation between CFHR-1/CFHR-3 deletion and altered aHUS and AMD risks, their work raises the possibility that other CFH-like (CFH-L1, derived from alternative splicing of the CFH gene) and CFH-related (CFHR-2 to CFHR-5, encoded by separate genes) plasma proteins may also possess complement-regulating activities. It also raises the question as to whether CFHR-1 might be involved in pathogen evasion of host immunity. Apart from protecting host cells from complement attack, CFH is frequently recruited and used by pathogens to thwart the host complement system. It has been shown previously that some pathogens can recruit and bind CFHR-1. Thus, it will be interesting to determine whether these organisms can use this and other CFHRs for immune evasion as well. It is hoped that the current study will serve as a catalyst to stimulate additional investigations into these questions.

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

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CLINICAL TRIALS

Comment on Greenberg et al, page 2393

Out of this nettle, danger, we must pluck this flower, safety

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In this issue of Blood, Greenberg and colleagues report the final results of the ECOG E1996 study, a randomized prospective clinical trial designed to assess both efficacy and safety of recombinant erythropoietin in patients with MDS.1

Erythropoiesis stimulating agents (ESAs) epoetin and darbepoetin are by far the most commonly prescribed drugs for patients with myelodysplastic syndrome (MDS).2 In part, this is because ESAs are recommended for treatment of anemia in lower-risk MDS patients by widely used clinical practice guidelines, such as those of the National Comprehensive Cancer Network (NCCN; www.nccn.org). Yet ESAs are neither approved for this indication by the US Food and Drug Administration (FDA), nor is long-term ESA safety well established in patients with MDS.1

ESA safety has received considerable attention during the past 4 years, as a number of concerns have arisen with respect to the risks of ESA exposure in patients with various neoplasms—concerns that emerged only after tens of thousands of patients with solid tumors were treated with ESAs.4 Worrisome safety data in patients with cancer-associated anemia have prompted the FDA to revise ESA labels multiple times, including addition of a series of sobering “black box” warnings to prescribing information. The FDA has also mandated that ESA spon-

sors must rigorously examine ESA risks in various patient populations.

The lack of a specific ESA label for MDS has had practical consequences for patients. In 2007, the Centers for Medicare and Medicaid Services (CMS) proposed a National Coverage Decision (NCD) that would have ended reimbursement for ESAs when used to treat MDS-associated anemia. CMS only backed down from this stance and revised the restrictive NCD to exclude MDS after a broad-based campaign advocating preservation of ESA access for MDS patients, supported by the American Society of Hematology (ASH), the American Society of Clinical Oncology, the MDS Foundation, the Aplastic Anemia & MDS Foundation, and other organizations. CMS ultimately left ESA coverage decisions for MDS up to regional carriers, which unfortunately means that ESA reimbursement policies vary from region to region—the sort of “postcode medicine” more commonly associated with nationalized health services in the United Kingdom and elsewhere than with health care delivery in the United States.

Various investigators have published results from open-label studies of ESAs in MDS, used either as single agents or in combination with colony stimulating factors (CSFs, for which there is in vitro evidence of synergistic effects on erythropoiesis), with major hemoglobin response rates ranging from 10% to 40%.5 6 But there are almost no prospective, controlled, randomized trials.

In this issue of Blood, Greenberg and colleagues help fill that data gap by presenting the final results of the Eastern Cooperative Oncology Group (ECOG) E1996 prospective clinical trial of ESAs for patients with MDS, which was first reported in abstract form at the ASH annual meeting in 2004 and is now published with a lengthy median follow-up time of 5.8 years. The investigators enrolled 110 patients with lower-risk MDS, who were randomized to receive either epoetin alfa, with or without filgrastim, or supportive care. The erythroid response rate was 34% for the active treatment arm using 2006 International Working Group criteria, compared with 5.8% for the supportive care arm.

ESA responders lived longer than nonresponders in the E1996 study, presumably because ESA responses mark patients who have
more hematopoietic reserve and less severe disease. Although overall survival and leukemic transformation rates were equivalent between E1996 randomization groups, crossover of the supportive care arm to active treatment after 4 months limits our ability to draw conclusions about longer-term safety of ESAs in MDS, and the study was also powered so that only quite dramatic survival differences could have been detected (ie, 80% power to detect a 46% difference in hazard rate).

Several recent retrospective studies suggested that ESA treatment may be associated with a survival benefit in MDS, but these encouraging retrospective analyses are potentially confounded by patient selection bias.7,8 It is clear that larger prospective studies with primary safety endpoints, including both overall survival and progression-free survival, are needed. However, as for Hotspur’s metaphorical dangerous nettle in Henry IV, Part I, actually conducting such studies to pluck the flower of safety is a tricky business, because of logistical hurdles, patient preferences, and entrenched practice patterns. An ambitious industry-sponsored controlled study of epoetin alfa in MDS, EPO-ANE-3018, began enrolling patients a few months ago (the accrual goal is 450 patients), but results will not be available for at least a few years. Therefore, E1996 represents an important contribution—not because it definitively answers all important ESA safety questions, but because it suggests that ESA exposure is relatively safe in MDS at least in the very short term—and because for several years to come, the E1996 results will remain virtually the only controlled data available in this area.

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Comment on Balgobind et al, page 2489

T(11q23): brand necessary

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A large intergroup investigation of MLL translocation partners in pediatric AML discovers low-risk star, t(1;11), confirms high-risk chromosomes 6 and 10 partners, and declares generic t11q23 insufficient for risk stratification.1

Risk-stratification of disease is a cornerstone of leukemia therapy. Rearrangements of the MLL gene on chromosomal band 11q23 are considered high-risk. Within MLL-rearranged leukemia, age, phenotype, translocation partner, and additional chromosomal aberrations are prognostic indicators in some studies.

To examine how MLL translocation partners and these other variables correlate with prognosis in pediatric acute myeloid leukemia (AML), in this issue of Blood, Balgobind and colleagues review outcomes of 756 children with confirmed MLL-rearranged AML treated on recent clinical trials of 11 collaborative groups from 15 countries.1 The 5-year event-free survival (EFS) is 44%1 and overall survival (OS) 56% in the MLL-rearranged cohort, the same as the respective medians for all AML treated after 1992 in these collaborative groups.1 Thus, generic MLL rearrangement appears to be an intermediate-risk type of pediatric AML.

Outcomes within the MLL-rearranged cohort vary significantly according to translocation partner ranging from 11% EFS in t(6;11)(q27;q23) rearrangement to 92% EFS in t(1;11)(q21;p23) rearrangement (see figure).1 In rearranged t(9;11) AML, EFS is 50%, that is, intermediate, although within the t(9;11) subset FAB M5 is a relatively favorable phenotype.1 Older age, additional cytogenetic aberrations, and leukocyte count more than 100 × 109/L are unfavorable.

The 5-year OS of 100% in the 3% of children with t(1;11)(q21;p23) is remarkable. The 1q21 partner gene, AF1q, encodes a proapoptotic mitochondrial membrane protein expressed in normal hematopoietic progenitors and variably expressed in AML and other cancers.2 In vitro AF1q overexpression confers resistance to doxorubicin,3 and overexpression is associated with poor prognosis in pediatric AML.4 The der MLL fusion partner forms an oncogenic protein; the der AF1q partner forms no protein.5 Comparison of the activity of der MLL fusion protein in t(1;11)(q21;p23) with those of less favorable translocations may explain their different sensitivities to therapy.

The heterogeneity of outcomes within MLL-rearranged AML implies that generic classification of AML as t(11q23) is no longer sufficient for risk stratification. However, for partner identification to become standard practice, it must be accomplished expeditiously and economically. The Balgobind study uses a combination of cytogenetics and complementary FISH and molecular techniques to identify all translocation partners; expert review is retrospective.1 An equally large collaborative investigation reported by Meyer et al uses long-distance PCR to characterize 384 pediatric and 376 adult cases of the MLL-rearranged AML or ALL.6 This method identifies all reciprocal MLL fusions and structural abnormalities and provides patient-specific PCR probes for monitoring minimal residual disease.7 If the Meyer study is validated in real time, long-distance PCR could
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