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MYELOID NEOPLASIA

Comment on Tarlock et al, page 1137

CEBPA bZip mutations: just a single shot

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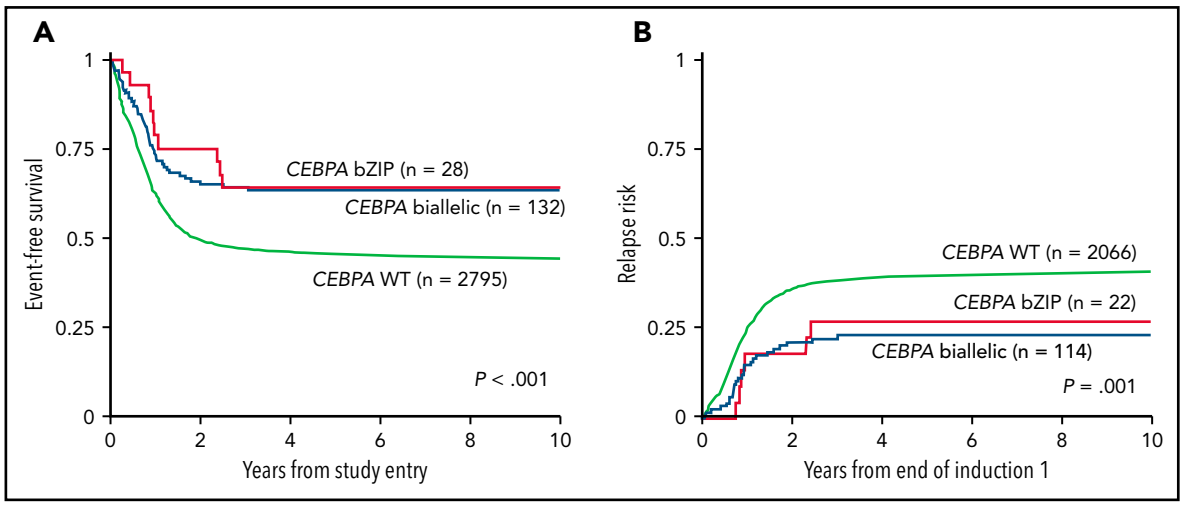
In this issue of *Blood*, Tarlock et al demonstrate that biallelic and single basic-region leucine zipper motif (bZIP) CCAAT enhancer–binding protein α (*CEBPA*) mutations have an equally favorable prognostic impact in acute myeloid leukemia (AML) in the largest reported series of children, adolescents, and young adults.[1]

In addition to its size (almost 3000 patients treated on consecutive Children's Oncology Group protocols), another strength of the study by Tarlock et al is the extensive molecular characterization of almost two-thirds of the patients using next-generation sequencing (NGS); in a fraction of cases, transcriptomic analysis was also performed. NGS allowed analysis of the frequency and prognostic impact of comutations in *CEBPA*-mutated and -nonmutated groups. An important finding of the study is that the presence of mutations in the cytokine receptor colony-stimulating factor 3 (*CSF3R*) gene, together with *CEBPA* biallelic or single bZIP *CEBPA* mutations, annuls the favorable impact on patient outcomes. Consistent with the equivalent prognosis of CEBPA biallelic and single bZIP CEBPA disease, gene and messenger RNA expression profiles of these 2 groups were comparable and different from those observed in *CEBPA* wild-type AML cases.

CEBPA is a transcription factor coded by an intronless gene located on chromosome 19. *CEBPA* mutations are detected in 7% to 15% of AML cases. *CEBPA* plays a pivotal role in normal granulopoiesis. It binds to regulatory sequences of multiple myeloid genes (*CSF3R*, *IL-6R*, *GFI-1*, *KLF1*). *CEBPA* has a carboxyterminal moiety with a bZIP motif. This bZIP motif binds to DNA and other transcription factors. By contrast, the amino-terminal region has 2 transactivation domains.

One-third of *CEBPA*-mutated AML cases shows a single involved allele, and two-thirds of patients have biallelic mutations.[2] On the basis of animal models and translational studies, it was thought that single mutations were insufficient to cause full leukemia. The observation of familial *CEBPA* leukemias reinforced the 2-hit model of *CEBPA*. Affected pedigrees usually transmit a single N-terminal mutation and require an additional lesion at the bZIP region for leukemia development.

Studies, mainly in adult patients, have so far supported that only biallelic *CEBPA* mutations confer improved event-free survival and/or overall survival in AML patients.[3-5] On the basis of the favorable prognostic impact of the mutations, the WHO classified *CEBPA* biallelic–mutated



Correlation between patients with *CEBPA* biallelic, *CEBPA* single bZIP mutation, and *CEBPA* wild-type (WT) AML. Event-free survival (A) and relapse (B). See Figure 3A-B in the article by Tarlock et al that begins on page 1137.

AML as a single clinical/biological entity in 2016.[6] European LeukemiaNet and National Comprehensive Cancer Network guidelines include this type of AML in their prognostic classification on the basis of the genetics in the favorable group.[7] Given the findings of the Tarlock et al report, should patients with single bZIP *CEBPA* mutations also be included in the good prognostic category of AML if these findings are confirmed in adults? Should *CEBPA*-mutated AML with comutations in *CSF3R* be removed from the favorable risk group? What is the prognosis of patients with biallelic or single bZIP *CEBPA* mutations with persistent minimal residual disease (MRD)? What is the prognosis of patients with *CEBPA*-mutated AML with comutations in *CSF3A* and negative MRD? Can the results of this pediatric and young adult series be extrapolated to adult patients with AML? These are open questions that must be answered in future studies.

The treatment recommendation for biallelic *CEBPA*–mutated AML in first complete remission is that hematopoietic transplantation is not indicated. However, at least 1 report has challenged this recommendation, because it showed better event-free survival in patients with biallelic *CEBPA*–mutated AML undergoing transplantation.[8] However, the retrospective nature of that study, the limited number of patients included, and the consistently good results with intermediate- or high-dose cytarabine consolidation without transplantation justify the chemotherapy approach as the treatment of choice for *CEBPA*-mutated AML in first complete remission. The data from Tarlock et al indicate that it seems reasonable to extend this approach to cases with single bZIP *CEBPA* mutations. In contrast, allogeneic transplantation would be an option if comutations in *CSF3R* were present.

The report presented here highlights the need of investigating comutations in *CEBPA*-mutated AML. NGS is increasingly being incorporated into routine diagnostic evaluations. Capillary electrophoresis focused on the *CEBPA* bZIP region combined with *CSF3R* analysis is another methodology to identify these 2 prognostic genes. Finally, the extended biological characterization of *CEBPA*-mutated AML is mandatory for introducing molecularly targeted therapies addressing comutations, such as *FLT3*, *IDH1*, *IDH2*, and the *CSFR3/JAK/STAT* signaling pathway genes. Clinical trials combining these agents with standard chemotherapy and/or novel agents may further improve the outcomes of patients with *CEBPA*-mutated AML (see figure).

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RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Liu et al, page 1162

Heme: driver of erythrocyte elimination

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In this issue of *Blood*, Liu et al[1] reveal that in sickle cell disease (SCD), hemolysis-derived heme triggers release of IFN-I, which ultimately results in increased liver macrophages that phagocytize antibody-coated erythrocytes (see figure) in both in vivo (mouse) and in vitro (human) models.

Heme is a crucial cofactor in aerobic metabolism. It fulfills its functions when bound to proteins and compartmentalized within cells. In vertebrates, heme is mostly found in erythrocytes where it performs gas transport as a part of hemoglobin. Despite its essential role, heme has a dark side. The presence of redox-active iron ion and its extensive hydrophobicity make it an inherently dangerous and toxic molecule.[2] Thus, heme manifests strong prooxidative and proinflammatory properties; it can interfere with coagulation and complement cascades and oxidize plasma lipoproteins in blood.[3,4] These activities of heme are particularly important when it is not bound to a protein. Considerable quantities of heme can be released as a result of hemolysis in various pathological conditions, such as SCD, thalassemia, hemolytic uremic syndrome, and autoimmune hemolytic anemia, among others. The capacity of cell-free heme to trigger proinflammatory states in different cell types, such as neutrophils, macrophages, endothelial cells, and platelets, and to activate the complement system has been postulated to contribute directly to the pathogenesis of the hemolytic diseases.[3,4] Mechanistically, it has been shown that heme serves as a ligand for the prototypic proinflammatory receptor