CEBPA resembles Roman god Janus

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In this issue of Blood, Ho and colleagues report the independent predictive value of single gene mutations in the CEBPA gene in pediatric acute myeloid leukemia. The outcome for this group of patients was excellent with 83% (± 13%) overall survival at 5 years from study entry.

The CCAAT/enhancer binding protein, encoded by the CEBPA gene, is a transcription factor that induces the expression of genes involved in terminal differentiation of granulocytes. Recently, CEBPA mutations have been added to the list of single-gene mutations that may define a separate disease entity in cytogenetically normal acute myeloid leukemia (CN-AML), which is increasingly recognized as a molecularly heterogeneous disease.1 Apart from CEBPA mutations, mutations in nucleophosmin (NPM1), in FMS-related tyrosine kinase 3 (FLT3), and in the Wilms tumor 1 (WT1) gene can be identified in CN-AML. In pediatric AML, the frequency of CN-AML is lower in comparison with adult AML, and accounts for only 20% to 25% of cases. Given the differences in overall outcome between adult and pediatric AML, the molecular classification and subsequent treatment stratification of CN-AML needs to be validated in separate pediatric studies. For FLT3, NPM1, and WT1, such data are currently available.2-4 Different NPM1 mutations were found in pediatric as compared with adult AML, underlining the need for separate studies in pediatric AML.

In this issue, Ho et al screen a large series of pediatric AML samples, obtained from 3 Children’s Oncology Group (COG) studies, for CEBPA mutations by fragment-length analysis.5 Acquired mutations were identified in 4.5% of all patients and clustered in CN-AML. In fact, 17% of pediatric patients with CN-AML were CEBPA-mutated. The majority of patients (82%) had “double” mutations in both the N-terminal domain and in the bZIP domain of the CEBPA gene. Patients with CEBPA-mutated AML showed similar survival rates as children with core-binding factor AML (ie, AML with inv(16) or t(8;21)). No differences in outcome were detected between double and single mutants, which is in contrast to Wouters et al, who recently reported that favorable outcome is restricted to patients with “double mutations,” which are usually localized on different alleles, resulting in the absence of wild-type protein.6 Recent data also suggest that accompanying genetic abnormalities may influence the prognostic impact of CEBPA mutations. For instance, Reneville et al showed that favorable outcome was restricted to patients with CN-AML without accompanying cytogenetic abnormalities or FLT3/ITD.7 Ho et al, however, found additional cytogenetic abnormalities in 14% of patients, with limited impact on outcome (overall survival 80% for patients with a normal karyotype, and 78% for all patients together).

CEBPA, however, may contribute to leukemogenesis in opposite ways, which led us to compare CEBPA with the Roman god Janus. According to Roman mythology, he was the god of doors and gateways and is typically displayed as having 2 faces looking in opposite directions. His name is already permanently associated with the Janus kinases, which are characterized by an inhibitory and activating kinase domain and are involved in Down syndrome leukemias and T-cell acute lymphoblastic leukemia. At least
23 examples of “Janus-like” behavior of CEBPA need to be mentioned. For instance, apart from loss of function of the CEBPA protein by mutations or by epigenetic silencing (see below), over-expression of the CEBPA protein may also be leukemogenic, as reported by Chapíro et al.3 They showed that CEBPA is overexpressed due to a juxtaposition to the immunoglobulin gene promoter in patients with B-cell precursor acute lymphoblastic leukemia with a specific chromosomal translocation. Another intriguing example is the difference in outcome between patients with CEBPA silencing by mutations versus those with epigenetic silencing (5-year overall survival 88% vs 25%, respectively).9,10 This occurs despite the fact that both patient groups display marked similarity in gene expression signatures. However, the clinical phenotype of the leukemias with epigenetic CEBPA silencing is distinct, with expression of T-cell markers and NOTCH1 mutations.10 Moreover, Figueroa et al demonstrated that these samples were characterized by more widespread hypermethylation, which was not restricted to the CEBPA network only.9 These data now await confirmation by other adult AML groups and in pediatric cohorts, which are lacking to date.

The next step is how to implement this knowledge into the clinic. Ho et al point out that, similar to patients with core-binding factor leukemias, patients with CEBPA-mutated AML should not be candidates for transplantation in first complete remission in future pediatric AML studies. This avoids the mortality and long-term morbidity with which this procedure is associated. Moreover, clinical studies need to be designed to assess whether the outcome of patients with epigenetic silencing can be improved by adding demethylating agents.

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REFERENCES


Dyskeratosis congenita (DC) is an inherited bone marrow failure syndrome (IBMFS) whose clinical spectrum has dramatically evolved over the past 10 years. Historically, patients were diagnosed with DC based on the association of BMF with the classic triad of mucocutaneous features including changes in skin pigmentation, dystrophic fingernails, and leukoplaikia. Over the past decade, germline mutations in 6 distinct genes, DKC1, TERC, TERT, NHP2, NOP10, and TINF2, were found to account for approximately 50% of patients with DC.1 The products of the DC genes all participate in telomere maintenance, revealing that defective telomere maintenance is the primary factor underlying disease pathogenesis. By the time DC patients develop BMF, all have short telomeres.2,3,4 With the availability of genetic testing, the clinical spectrum of DC has broadened, and it has become clear that the initially described mucocutaneous manifestations are present in only a small proportion of patients, generally those with a more severe phenotype and an earlier onset of disease (see figure).

It has also become evident that the inheritance of DC is complex, with X-linked, autosomal dominant, and recessive pedigrees.1 Furthermore, DC may occur sporadically due to the presence of de novo germline mutations in a single allele of a DC-associated gene. Finally, in some families with autosomal dominant DC, the inheritance of successively shorter telomeres is associated with genetic “anticipation,” characterized by progressively more severe disease manifestations at younger ages with each generation.1,5,6 This genetic heterogeneity is associated with a wide clinical spectrum that ranges from intrauterine growth retardation or death in early childhood to no overt features of disease (see figure). The variability in clinical features and complexity of genetics presents a unique challenge to physicians and genetic counselors confronted with patients suffering from DC, silent mutation carriers, or family members of affected individuals.

The cancer risk assessment presented by Alter et al is based on patients reported in the literature since 1910,7 which primarily includes patients with a classic presentation and a relatively severe phenotype (see figure). In addition, the authors include the NCI cohort, which consists of families with at least one affected family member, persons with a very

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Cancer & inherited bone marrow failure states

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In this issue of Blood, Alter and colleagues report on the spectrum of cancers occurring in 500 patients with DC as reported in the medical literature from 1910 to 2008 and in a prospective cohort of 50 DC patients followed at the National Cancer Institute (NCI). The study finds in both cohorts a cumulative incidence of cancer approximating 40% to 50%, as well as a shortened overall survival and a poor outcome after HSCT. Squamous cell carcinomas of the head and neck were the most frequently noted cancers in both study populations followed by skin, anorectal, and other cancers.

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