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. Apart from *CEBPA* mutations, mutations in nucleophosmin (*NPM1*), in FMS-related tyrosine kinase 3 (*FLT3*), and in 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. 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. 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. 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*. 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
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 approximately 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.

**REFERENCES**


**Comment on Alter et al, page 6549**

**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.
CEBPA resembles Roman god Janus

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