be an early somatic event in radiation-driven breast transformation. c-MYC and PVT1 are almost always amplified together in human tumors, and the PVT1 long noncoding RNA was recently identified as a key regulator of MYC-driven oncogenic transcriptional activity by augmenting protein stability8 (see figure). There is also evidence that the PVT1 promoter directly regulates MYC transcription, independent of long noncoding RNA expression.9 Knockout of PVT1 reduces MYC protein levels and attenuates tumorigenic potential of cells.9 Other data also suggest a role for dysregulated MYC in radiation-induced breast transformation. Specifically, Best et al identified a SNP in the PRDM1 gene associated with radiogenic cancer risk (predominantly breast cancer) in pediatric Hodgkin lymphoma survivors. PRDM1 is a negative regulator of c-MYC transcription, but PRDM1 upregulation in response to ionizing radiation is attenuated in cells carrying the risk variant, leading to elevated c-MYC expression and acquisition of a pro-proliferative phenotype.5 Collectively, these studies provide compelling evidence that dysregulated MYC is a common feature of radiogenic breast cancer during the early stages of transformation. As such, it is plausible that the PVT1 SNP identified by Opstal-van Winden et al also operates via MYC to affect risk of radiogenic breast cancer, although additional work is required to determine functionality of the rs10505506 variant.

Pending independent validation, the data presented by Opstal-van Winden and others could aid the development of personalized risk-adapted strategies for the clinical management of Hodgkin lymphoma patients, including alternative treatments and posttherapy surveillance for therapy-induced breast cancer. Such approaches could prove important in pediatric and young adult Hodgkin lymphoma patients where the risk of radiogenic breast cancer is particularly high and associated with premature death.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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MYELOID NEOPLASIA

Comment on Christen et al, page 1140

More than a fusion gene: the RUNX1-RUNX1T1 AML

Torsten Haferlach and Manja Meggendorfer | MLL Munich Leukemia Laboratory

In this issue of Blood, Christen et al investigated the largest cohort to date of 331 patients with acute myeloid leukemia (AML) and t(8;21).1

These patients have AML with specific morphologic features such as dysplasia in granulopoiesis (90% of patients) and eosinophilia and are mostly classified as AML with maturation (90%; formally called French-American-British [FAB] M2) or AML without maturation (10%; formally called FAB M1).2 This subtype of AML is also diagnosed by immunophenotyping that shows the coexpression of CD19 or PAX5 and CD56. The cytogenetics show a typical pattern of loss of the sex chromosome and del(9q). These characteristics resulted in RUNX1-RUNX1T1-mutated AML being designated as a separate World Health Organization (WHO) entity within the category of AML with recurrent genetic abnormalities. The diagnosis is made irrespective of bone marrow blast cell counts.3 RUNX1-RUNX1T1–mutated AML also demonstrates secondary cooperating mutations in KIT, KRAS or NRAS, and ASXL1 as well as in ASXL2.4,5 RUNX1-RUNX1T1 was one of the first fusion genes to be used for minimal residual disease (MRD) monitoring.6 Based on these diagnostic definitions, the best clinical practice to follow after standard chemotherapy needed to be determined, including the meaningfulness of allogeneic transplantation in first complete molecular remission (CMR).7,8

Today, large sequencing studies including exome sequencing or whole-genome sequencing (WES) are possible. In their article, Christen et al provide a comprehensive characterization of this specific WHO entity in 331 patients based on a screening that included 66 recurrently mutated genes. They found that 95% of patients had at least 1 additional mutation, with a mean of 2.2 driver mutations per patient. Recurrently mutated genes affecting the RAS/RTK signaling pathway were present in nearly two-thirds of patients and other epigenetic regulators in nearly half the patients. Several previously unexpected genes were found to be mutated. Data using deep sequencing (45,000×) in 62 samples from patients in complete remission demonstrated persistent mutations in 12 samples, including 5 patients who were quantitative polymerase chain reaction–negative for RUNX1-RUNX1T1 at the time of the analysis. In multivariate analysis, JAK2, FLT3-ITDhigh, and KITThigh were identified as significant negative prognostic factors. Furthermore, it was demonstrated that one-third of patients...
studied by WES both at diagnosis and at relapse were genetically unstable and did not fully reproduce the genetic landscape of the diagnostic sample at relapse. Therefore, this comprehensive study clearly demonstrates that patients with AML and t(8;21) at diagnosis should, according to WHO gold standards, be studied by morphology, immunophenotyping, and cytogenetics. In addition, a molecular genetic screening (targeted sequencing) will become important.

findings at relapse may have implications for prognosis and especially any targeted treatment. This may be of particular importance for patients in CMR for RUNX1-RUNX1T1 but with secondary mutations still detectable in low levels (see figure).

Because the capacity for panel sequencing and WES will increase rapidly worldwide over the next few years, AML with RUNX1-RUNX1T1 should be comprehensively investigated at diagnosis, during follow-up for MRD monitoring, and at relapse to individualize treatments, including targeted approaches toward driver genes. Genetics at relapse can hold additional important information. This study definitely sets the stage.

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

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