

Clinical Importance of Genetic Findings in Adult AML

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Cytogenetics are now routinely used in selecting therapy for patients with acute myeloid leukemia (AML). Multiple large prospective studies have shown the independent prognostic significance of pretreatment karyotype findings in adult AML using modern therapeutic approaches. Indeed the importance of genetics in classification has been recognized in the new World Health Organization (WHO) classification of AML which requires cytogenetic or molecular identification of the presence of the t(15;17)(q22;q12) or PML/RARA; t(8;21)(q22;q22) or AML1/ETO; inv(16)(p13q22) or t(16;16)(p13;q22) or CBFb/MYH11; and balanced translocations involving 11q23 (rearrangement of MLL).

The importance of identification of the above specific abnormalities for selecting therapy has been confirmed in many recent studies. Long-term follow-up suggests that approximately 70% of patients with t(15;17) are cured with tailored therapy combining all-trans retinoic acid and anthracycline containing chemotherapy regimens. The second most favorable cytogenetic group is Core Binding Factor (CBF) AML which includes t(8;21) and inv(16). CBF AML appears to benefit from regimens containing higher doses of cytarabine. Among the 11q23 translocations, only those involving t(9;11)(p22;q23) appear to be long-term survivors in the absence of stem cell transplantation (SCT).

Normal cytogenetics constitute 45% of de novo adult AML, and intensive efforts to classify these patients molecularly are on-going. Molecular studies include ones exploring the added use in predicting benefit from standard therapy of identification of the partial tandem duplication (PTD) of MLL, analysis of the FLT3 internal tandem duplication (ITD), epigenetic profiling using restriction landmark genomic scanning (RLGS) to

assess gene methylation and gene expression array results. Recent studies have shown an adverse prognosis when the PTD of MLL is found and when FLT3 ITD coexists with loss of FLT3 wild-type allele. Therapies that specifically target these molecular abnormalities are under development.

A number of specific cytogenetic abnormalities are associated with very poor clinical outcomes. Two relatively common non-specific cytogenetic groups with poor clinical outcomes include isolated trisomy and complex karyotypes. Trisomy as a sole abnormality occurs in approximately 7% of adult de novo AML patients. Such patients have a significantly inferior outcome compared to patients with normal cytogenetics. SCT appears to improve outcome in patients <60 years.

Complex karyotype has been defined differently among groups with some defining complex based on at least 5 clonal aberrations and others at least 3 in the absence of CBF AML, t(15;17) or t(9;11). Secondary aberrations and a complex karyotype do not adversely affect outcome of patients with CBF AML, or t(9;11). In patients with other cytogenetic abnormalities the presence of 5 or more abnormalities appears to carry a significantly worse prognosis than the presence of 3 or more abnormalities. However, patients with 3 or more abnormalities also do poorly and have a significantly inferior outcome compared to patients with normal cytogenetics. Whether this relates to specific cytogenetic abnormalities or to other genetic or epigenetic abnormalities is currently unclear.

In addition to being used to select therapy, genetic analyses are being studied for their use in defining complete remission and detecting residual disease or

early relapse. We have recently provided data that suggests that documentation of cytogenetic remission at the time of hematologic complete remission should be considered in patients presenting with abnormal karyotypes. In patients with acute promyelocytic leukemia (APL) several studies have shown the importance of detection of the persistence or reappearance of the PML/RAR α transcript for determining the need for additional therapy while the patient is in hematologic complete remission.

The use of all-trans retinoic acid for APL is the best current example of the way in which molecularly tar-

geted therapy has changed the outcome of a specific type of AML. Imatinib mesylate is now being investigated in AML with t(9;22)(qq34;q11) with some success. Although genomics and proteomics are in their infancy in AML, they will almost certainly add significantly to our understanding of leukemogenesis, our ability to predict outcome and the identification of new molecular targets. The rapid advances in understanding the molecular basis of AML suggest that molecularly targeted therapy will soon be a reality for many patients.