fusion? Third, the effects of STX11- or MUNC18B-deficiency on lysosome secretion are much more modest than those on α or dense granule release,12 implying distinct controls for secretion from lysosomes relative to dense and α granules. Either of 2 models might explain this phenomenon: either the effects on lysosomal secretion are indirect (e.g., a consequence of reduced signaling because of the lack of ADP release from dense granules) and a distinct syntaxin isoform, such as the less abundant STX7, participates in lysosome secretion, or lysosomal secretion is mediated by a set of redundant syntaxins. Finally, if release of dense and α granules (and to at least some extent, lysosomes) is under similar molecular control, then how does one account for the different kinetics of their release after platelet stimulation? Surely the answers to these questions will be unlocked in the years ahead.

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Comment on Middeke et al, page 2521

AML cytogenetics: the complex just got simpler

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In this issue of Blood, Middeke et al, for the well-regarded Cooperative German Transplant Study Group, report a retrospective analysis in which they demonstrate that a hierarchical classification system for specific cytogenetic abnormalities in acute myeloid leukemia (AML) reveals that patients with abnormal 17p [abnl(17p)] and −5/5q− abnormalities have worse outcomes after allogeneic hematopoietic cell transplantation (HCT).1

Further, if these cytogenetic abnormalities are excluded, then complex karyotype (CK) and monosomal karyotype (MK) lose their predictive value. In the article by Middeke and colleagues, Figure 2A and B demonstrate no outcome differences between those patients with (CK+) and without (CK−) complex cytogenetics, and with (MK+) and without (MK−) monosomy cytogenetics, when abnl(17p) and −5/5q− are removed.1

The cytogenetic profile of AML at diagnosis consistently remains a highly influential prognostic factor even though the standard backbone of induction therapy largely has remained unchanged for 4 decades. Many of the improvements in prognosis for AML patients during this time are a reflection of the use of appropriately applied risk-adapted and intensified treatment strategies, including allogeneic HCT. In the United States, AML with the presence of a clone with at least 3 unrelated clonal cytogenetic abnormalities,2 often designated as a complex karyotype, has been universally considered as unfavorable and associated with one of the poorest patient outcomes. Complex karyotype in the United Kingdom has been defined as 5 or more abnormalities.3 Those patients with monosomal karyotypes were reported to have a 4% overall survival at 4 years, compared with 26% for those without this cytogenetic feature, a result similar to the particularly unfavorable outcome noted by Medeiros et al for the Southwest Oncology Group where the 4-year survival was only 1%.4

The German investigators retrospectively analyzed a recent cohort (2005–2008) of 236 first complete remission patients. Nearly half (49%) received reduced-intensity conditioning HCT; the graft source was sibling-matched in approximately one-quarter (26%), and matched unrelated donor in nearly half (49%). All had high-risk European LeukemiaNet (ELN) cytogenetic abnormalities including 70 ELN intermediate-2 and 166 ELN adverse-risk. This hierarchical approach was a more discriminative prognostic tool than the complex or monosomy cytogenetics. Two-year event-free survival (EFS) was only 11% in those with abnl(17p), 29% in patients with −5/5q− (but not abnl(17p)), but was 49% in the remaining high-risk cytogenetic group (without these 2 features).

The major reason for treatment failure was relapse. As with all publications that describe potentially practice-changing findings, the Middeke et al study must be validated using other cohorts of patients and hopefully with a larger patient population, both in the HCT...
Event-free survival (EFS) in patients with adverse-risk karyotypes classified by monosomal karyotype (MK), complex karyotype (CK), or monosomy 7 after exclusion of acute myeloid leukemia (AML) with either of the 2 marker lesions abnl(17p) or −5/5q.−. (A) EFS at 2 years was 53% (95% confidence interval [CI], 30%-76%) in 19 patients with MK− AML compared with 48% (95% CI, 36%-60%) in 76 patients with MK+ AML. (B) EFS at 2 years was 47% (95% CI, 31%-63%) in 38 patients with CK+ AML compared with 51% (95% CI, 37%-73%) in 57 patients with CK− AML. See Figure 2 in the article by Middeke et al that begins on page 2521.1

and non–HCT settings. A comparison with other prognostic schemes for predicting outcome would be of significant interest.2 It is worth noting that in a preliminary communication for the Eastern Cooperative Oncology Group, Strickland and coworkers found that aberrations of chromosomes 5 and 7 aberrations failed to add prognostic significance to monosomal cytogenetics.4 Do these differences in prognostic significance vary as a result of the treatment modality, or are they a consequence of age, as the patient population Strickland et al reported included older adults while the Germans enrolled mostly younger patients, under 60 years of age? Further, the German group does not provide the description of the breakpoints in the 5q deletion; a distinct tumor suppressor gene is proposed to be located at the 5q13.3 locus.

Given these data, how should a clinician now approach such AML patients? The German authors question the role of allogeneic HCT and the great financial and potentially high morbidity and mortality costs and recommend alternative strategies in these high-risk patients. But are they correct? Certainly their observation provides an additional stratification for advising patients and physicians alike about prognosis as relapse was the major cause of failure. While restoration of the defective cytogenetic functions is the most important goal, over the past decade there have been many exciting targeted, specific, and molecular approaches; however, the overall survival curves for patients 60 years of age or younger published by most groups have not changed.

Such data suggest that inherent resistance, or alternative, resistance mechanisms are in place that may prevent a dramatic outcome to a specific single target. At present, there are no obvious pharmacologic candidate agents under clinical study to address these targets; allogeneic HCT remains an effective antileukemia strategy in some patients who are not otherwise curable. Further, this approach theoretically could be enhanced by application of the addition of newer agents already in clinical practice, several of which have been applied to other malignant disease targets. Candidate agents worthy of study include mTOR inhibitors that double as anti–graft-versus-host disease prophylaxis agents (sirolimus),7 use of postremission agents including hypomethylating or histone deacetylase inhibitors,4 or bispecific monoclonal antibodies as is being applied in acute lymphoblastic leukemia.8 One of the most exciting targeted agents is a small molecule that inhibits the DOT1L histone methyltransferase for the 11q23/MLL gene, that is, targeting the molecular defect; clinical trials are about to commence.10 Until then, this new cytogenetic observation may have simplified the process of identifying the most high-risk AML patients.

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