Acute Myeloid Leukemia: The Challenge of Unfavorable Cytogenetics

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Disease Categorization

Prognostic factors in acute myeloid leukemia (AML) may be subdivided into those related to patient characteristics and general health condition, and those related to characteristics of the tumor.[1] Among the AML-related factors, the karyotype of the leukemic cells is the strongest independent prognostic indicator for response to therapy and for survival, and allows one to stratify patients into three cytogenetic risk groups: favorable, intermediate, and unfavorable.[1-4] The article by Drs. Orozco and Appelbaum gives an informative and systematic overview of biologic characteristics and treatment options for AML with unfavorable cytogenetics, focusing in particular on AML with complex and monosomal karyotypes.

While biologically different, all types of AML with unfavorable cytogenetic findings have a relatively poor outcome with currently available treatments.[1] However, two overlapping subgroups within the unfavorable risk category, AML with complex cytogenetics and AML with monosomal karyotype (MK), pose additional challenges.[5,6] The incidence of these subtypes increases with age, so that they are frequently encountered in older patients who more often have comorbidities and poor performance status, and thus are not candidates for intensive remission induction therapy and hematopoietic stem cell transplantation (HSCT).[7] Additionally, for reasons that still await biologic and molecular explanation, MK-AML appears associated with a particularly poor outcome.[8]

Drs. Orozco and Appelbaum offer a helpful overview of cytogenetic risk classification schemes developed over a period of almost 2 decades by large collaborative groups: the Southwest Oncology Group (SWOG), the Medical Research Council (MRC), and Cancer and Leukemia Group B (CALGB). Differences in classification schemes are relatively minor, and can be explained by the different patient populations enrolled in the SWOG, MRC, and CALGB trials, as well as by differing treatments. In addition, CALGB applies separate classification schemes depending on whether the outcome is measured by complete response rate (CR), relapse risk (RR) after CR, or overall survival (OS), to reflect the fact that abnormalities predicting, for example, resistance to induction therapy may differ from the ones predicting high risk of relapse. Importantly, all three classification schemes distinguish the three major prognostic groups (favorable, intermediate, and unfavorable) with good concordance regarding the cytogenetic abnormalities that predict favorable [t(8;21), inv(16)] as well as unfavorable outcome [complex karyotype, abn(3q)].[2-4,9]

More recently, the characterization of a number of molecular markers has allowed further refinement of risk stratification in AML.[10] At this time, however, molecular profiling does not appear to offer additional prognostic information for patients with unfavorable risk cytogenetics. Systematic evaluation for an increasing number of nonrandom mutations in AML has allowed better stratification of AMLs with normal cytogenetics (CN-AML), which represent a large proportion (almost 50%) of newly diagnosed cases.[11] The recently proposed European Leukemia Network (ELN) classification uses the presence of the FLT3-ITD mutation, as well as CEBPA and NPM1 mutation status, to stratify AML with intermediate-risk cytogenetics, including CN-AML.[12] This classification uses the molecular markers to subdivide the intermediate-risk AML into a more favorable Intermediate-I and a less favorable Intermediate-II category. The prognostic value of this risk classification has been tested on two large cohorts of patients (the AML96 trial and CALGB patient cohorts), and the data suggest that this may be the best system for outcome prediction in AML available to date.[12,13] Undoubtedly, this genetic classification will evolve as new recurring mutations are discovered that influence the outcome of AML treatment.

In addition to implementation of molecular markers, the increased use of HSCT has an impact on risk
stratification and outcomes in AML. It is important to remember that the current classification schemes are based on historical SWOG, CALGB, and MRC trials that used chemotherapy as the main treatment modality; it remains to be seen whether HSCT can overcome the adverse effects of some high- and intermediate-risk karyotypes.

Regarding the biology and molecular pathogenesis of unfavorable-risk AML, the association of a complex karyotype with poor prognosis comes as no surprise. In cancer cytogenetics, karyotype complexity has traditionally been considered as a sign of clonal evolution and high mutation load, particularly in the presence of multiple related abnormal clones. The high incidence of complex karyotypes in older patients, and in AML with myelodysplastic changes, AML evolving from myelodysplastic syndrome (MDS), and therapy-related AML, suggests that AML with complex karyotype results from the accumulation of large numbers of mutations as patients age, as they are exposed to mutagenic agents, or as hematopoiesis becomes increasingly more disordered in a MDS clone.[7,14]

It is more challenging to hypothesize about molecular mechanisms responsible for the progressive course in AML with isolated unfavorable cytogenetic abnormalities, such as t(6;9), which are often seen in younger patients, and in which cases a limited number of mutations appears sufficient to result in an aggressive and chemotherapy-resistant disease.[15] Similarly puzzling is the recently described category of AML with MK, and its reportedly dismal prognosis.[6,8] The uniqueness of this category is controversial, because of its substantial overlap with complex-karyotype AML and AML with monosomy 7, both of which are well recognized unfavorable categories. However, several studies support MK as a predictor of a particularly poor outcome, independent of complex karyotype. A recent SWOG analysis found that the 4-year survival for patients with complex cytogenetics but without an MK was 13%, but for those with an MK it was only 3%.[16] Clearly, both of these outcomes are quite poor.

**Therapy: Focus on Allogeneic HSCT**

Clinical trials that tested various modifications of the standard “cytarabine plus an anthracycline” induction regimen, such as increasing the anthracycline dose, or the use of alternative anthracyclines, high-dose cytarabine, or additional agents given with conventional 7+3 chemotherapy, have demonstrated little or no advantage for AML patients with unfavorable cytogenetics.[17-21] In contrast, improved outcomes following allogeneic HSCT have been clearly documented for younger adults with unfavorable cytogenetics, and more recently, for patients with MK-AML.[22-26] HSCT is recommended for young patients with poor-risk AML, and the question has shifted to how to make it more feasible and more effective for a higher proportion of these patients. Data from single centers and transplant registries show that outcomes after transplants from HLA-matched unrelated donors are similar to those from matched siblings.[27,28] In addition, although transplant-related mortality is higher with use of cord-blood transplants or alternative donors, relapse rates among transplanted patients are decreased compared with those given chemotherapy alone, leading to better long-term survival.[29] Therefore, it may soon be possible to offer transplantation to almost all young patients with high-risk AML who achieve a CR. Additionally, non-myeloablative and reduced-intensity conditioning regimens are increasingly making HSCT an option for older patients and those with comorbid conditions, although further studies are necessary to demonstrate a survival advantage of HSCT over chemotherapy for fit but older patients with high-risk AML.[30,31]

Many older patients with complex-karyotype, MK, and other high-risk–karyotype AMLs, however, are not candidates for either HSCT or intensive chemotherapy. Their treatment options are quite limited and unproven. Clinical trials of novel therapeutics should be recommended. Palliative treatment with clofarabine (Clolar), azacitidine (Vidaza), or decitabine (Dacogen) can achieve some disease control.[32-34] Finally, one must not forget that even with all available forms of therapy, including HSCT, the outcomes for unfavorable-risk AML remain generally poor. The obvious question becomes that of what the prospects are for developing completely novel therapeutic approaches, at least for some categories of unfavorable-cytogenetics AML. As nicely discussed in this review article, for subsets of high-risk AML, such as t(6;9) AML, in which a limited number of mutations may be driving the disease, it may be feasible to develop specific inhibitors of the key molecular pathways involved in leukemogenesis and the survival of leukemia stem cells.[15] However, development of effective small-molecule inhibitors will be a challenge for AML with more complex karyotypes and MK-AML, which appear to be associated with higher mutation burdens, frequently carry TP53 mutations,
express anti-apoptotic proteins, and commonly display multidrug resistance. Immune-based therapies merit investigation, as they might offer some benefit to patients in these most challenging categories of AML.[35]

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### References


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