Unfavorable, Complex, and Monosomal Karyotypes: The Most Challenging Forms of Acute Myeloid Leukemia

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Although the overall prognosis for patients with acute myeloid leukemia (AML) associated with unfavorable, complex, or monosomal karyotypes is poor, some patients can be cured.

Introduction

The karyotype of the leukemic cell is the strongest prognostic factor for response to induction therapy and survival in acute myeloid leukemia (AML). Three cytogenetic risk groups based on treatment outcomes exist: favorable, intermediate, and unfavorable. These groups account for 20%, 50%, and 30% of cases of AML, respectively. Overlapping subgroups within the unfavorable risk category include AML with complex cytogenetics and monosomal karyotype AML. The problem of AML with unfavorable-risk cytogenetics deserves special attention: this category of disease is a difficult clinical challenge, and the most appropriate therapeutic option may vary greatly—from the most aggressive we have to offer for some patients, to palliative care for others.

Disease Categorization

TABLE 1

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<th>Acute Myeloid Leukemia Cytogenetic Risk Classification</th>
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Favorable, intermediate, and unfavorable cytogenetics

The Southwest Oncology Group (SWOG), the Medical Research Council (MRC), and Cancer and Leukemia Group B (CALGB) each developed and adopted cytogenetic risk classifications more than 2 decades ago based on the outcomes of large prospective clinical trials.[1-3] Because the studies involved different patient populations and different treatments, it is not surprising that the resulting classifications, while similar, are not identical. For example, as shown in Table 1, in the SWOG categorization, patients with clonal abnormalities not recognized as within one of the three major groups are assigned to a fourth category with a predicted treatment outcome somewhere between the intermediate and unfavorable risk groups. CALGB’s risk categorization differs somewhat depending on whether one is interested in complete response (CR) rate, relapse risk, or overall survival (OS) (details not shown). There are also minor differences between classification schemas in the distinction between intermediate- and unfavorable-risk cytogenetics. More recently, in 2010, the MRC revised their classification system, with the major change being the movement of patients with various translocations involving chromosome 11 [with the exception of t(9;11) and t(11;19)] from the intermediate risk group into the unfavorable group.[4]

While these classification schemas differ slightly, they are each able to distinguish three major groups of patients. Among patients younger than 65 years treated with standard chemotherapy, those with a favorable karyotype have CR rates in the 85% to 90% range and a 5-year OS of 50% to 60%. Those with intermediate-risk cytogenetics have CR rates of 65% to 75%, and a 5-year OS of
35% to 45%. For patients with unfavorable-risk cytogenetics, a CR rate of 45% to 55% and a 5-year OS of only 10% to 20% can be expected.[1-4]

Complex karyotypes

In some cases of AML, multiple unrelated cytogenetic abnormalities will be seen in a single karyotype. If the number of abnormalities is sufficient, such cases are defined as having “complex” cytogenetics. In the case of SWOG and CALGB, three or more abnormalities are required for this definition, whereas the MRC requires four or more abnormalities for the cytogenetics to be considered complex. If these multiple abnormalities accompany one of the favorable-risk translocations, inv(16) or t(8;21), then CR rates and OS are slightly poorer than those seen in patients with the favorable-risk translocations alone, but they are still better than what would be expected with intermediate or unfavorable risk.[5] Thus, cases with inv(16) or t(8;21) and complex cytogenetics remain within the favorable-risk group and are not considered as “complex” in most discussions. All other cases with complex cytogenetics are defined as unfavorable, and make up between a third and half of all cases of unfavorable-risk disease, or 10% overall. In the analysis that led to the MRC’s recent revision of their classification system, investigators found that with each additional abnormality seen in a karyotype, the risk of failing to achieve a CR increased (hazard ratio [HR] = 1.42), as did the risk of mortality (HR = 1.19). Thus, patients with four abnormalities did worse than those with three, and those with five or more did worse than those with four. In the SWOG analysis, it was found that patients with complex cytogenetics but without involvement of either chromosomes 5 or 7 had a CR rate of 50% and an OS of 20%, while patients who had complex cytogenetics and involvement of chromosomes 5 or 7 had a CR rate of 37% and only 3% OS.

Monosomal karyotype

The finding of a single monosomy is relatively common in AML, with monosomy 7 being the most frequent. The presence of a single monosomy (excluding loss of a sex chromosome) is associated with a negative outcome, with a 12% OS at 4 years in the Dutch experience.[6] Patients with two or more distinct monosomies, or a single monosomy but with an additional structural abnormality, have an even worse prognosis, with a predicted 4-year survival of less than 4%.[6,7] Thus, this category of patient (two monosomies or one monosomy plus an additional structural abnormality) has been defined as having a “monosomal karyotype.” This group of patients has a very dismal prognosis if treated with conventional chemotherapy.

Various Cytogenetic Subsets of Acute Myeloid Leukemia

There is obvious overlap among patients with unfavorable, complex, and monosomal karyotypes. All patients with complex karyotypes, except those with inv(16) and t(8;21) fall within the unfavorable risk group and comprise between a third and half of the total. Also, virtually all (98%) of the patients with monosomal karyotypes fall in the unfavorable risk group and most (95%) have complex abnormalities. Monosomal karyotype AML accounts for about 40% of unfavorable-risk AML and two-thirds of cases with complex cytogenetics (see Figure 1). A recent SWOG analysis found that the 4-year OS of patients with complex cytogenetics but without a monosomal karyotype was 13%, but with a monosomal karyotype it was only 3%.[7]

Biology of Unfavorable-Risk Cytogenetics

Specific mutations associated with unfavorable-risk AML

Unfavorable-risk AML likely represents many different biologic syndromes. A number of specific genetic abnormalities are included in this category of disease. For example, t(6;9) is an uncommon translocation seen in about 1% of AMLs that results in a chimeric fusion gene between DEK (6p23) and CAN (9q34).[8] Inv(3) or t(3;3) is seen in about 1% of AMLs and involves
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**Integrated genetic profiling**

An increasing number of non-random mutations have been found in AML of all risk categories. A recent analysis tested for mutations in TET2, ASXL1, DNMT3A, CEBPA, PHF6, WT1, TP53, EZH2, RUNX1, and PTEN in a series of 502 patients.[11] This genetic profiling did not appear to offer additional diagnostic information for patients with unfavorable-risk cytogenetics. However, there were several categories of patients who are normally considered to have intermediate-risk disease who could be reclassified as high risk based on this analysis, including those without FLT3 mutations who have mutated TET2, mutated ASXL1, mutated PHF6, or MLL partial tandem duplications (PTD), and those who have FLT3 mutations with mutant TET2, DNMT3A, or MLL PTD.

**Clonal architecture of unfavorable-risk AML**

Several clinical and recent laboratory insights are providing a somewhat better picture of the development of at least some cases of unfavorable-risk AML. We know that the incidence of AML with unfavorable-risk cytogenetics increases as patients age, rising from around 30% in patients less than 55 years of age to more than 55% in those over age 75.[12] Additionally, in a comparison of treatment-related AMLs vs de novo AMLs, the chromosomal abnormalities that are over-represented in treatment-related AMLs are abn(17p), abnormalities in chromosomes 5 and 7, complex karyotypes, and monosomal karyotypes.[13] This listing of abnormalities almost exactly duplicates those that increase most with aging. Laboratory studies employing genome-wide copy-number analysis have found frequent somatic copy-number alterations not detectable on routine cytogenetic analysis, and perhaps not surprisingly, these additional abnormalities were more commonly found in patients with abnormal karyotypes.[14] Very recently, the group from St. Louis performed whole-genome sequencing of paired samples of skin and bone marrow from patients with AML that evolved from a prior myelodysplastic syndrome (MDS).[15] They were able to show that nearly all of the bone marrow cells in patients with MDS are clonally derived, and that the evolution of AML from MDS is the result of multiple cycles of mutation acquisition and clonal selection. The picture we are left with, then, is that there may be some cases of unfavorable-risk AML, such as those associated with t(6;9), in which a limited number of mutations may be sufficient to result in the disease. For such cases, one can hope that small-molecule inhibitors might be found. However, most cases of unfavorable-risk AML are likely the result of the accumulation of large numbers of mutations as patients age, with the development of progressively more disordered hematopoiesis and the eventual emergence of leukemia with multiple subclones. The development of effective small-molecule inhibitors for such AML patients will be a challenge.

**Therapy**

**Patient selection**

Many treatment guidelines for AML provide separate suggestions for patients younger or older than an arbitrary age cutoff, usually around 60 years, based on the implicit assumption that younger patients can tolerate more intensive therapy than their older counterparts. We recently questioned this assumption by examining the outcome of therapy in 3,365 patients with AML; a multicomponent model that accurately predicted treatment-related mortality was created and included information such as age, performance status, platelet count, and whether patients had primary or secondary disease, among other factors.[16] While age was a component of the model, eliminating age from the model only minimally affected the model’s accuracy. Thus, recommendations for initial induction...
therapy should be based on whether patients are eligible for intensive therapy or not, and not on age as per se. We have conducted similar studies for patients undergoing allogeneic hematopoietic cell transplantation (HCT) for AML, and again, a co-morbidity index proved to be a more important predictor of treatment outcome than age.[17]

**Induction**

Standard induction chemotherapy for adults with newly diagnosed AML consists of an anthracycline plus cytarabine. Recent studies have addressed the most appropriate dose of anthracycline and cytarabine, as well as whether other drugs added to the standard combination can improve outcome. Investigators from the Eastern Cooperative Oncology Group (ECOG) asked whether a higher dose of daunorubicin (at a dosage of 90 mg/m²/d for 3 days) was better than a lower dose (45 mg/m²/d for 3 days), both given in combination with standard cytarabine in patients younger than 60 years of age.[18] The higher dose was associated with a higher CR rate and improved OS. The impact of the higher dose anthracycline was greatest in those with favorable-risk and intermediate-risk disease. When the analysis was restricted to patients with unfavorable-risk cytogenetics, the improvement with higher-dose daunorubicin was much less but still tended in the same direction. The Dutch Haemato-Oncology Foundation for Adults in the Netherlands (HOVON) group conducted a similar study in patients 60 to 83 years old.[19] Among patients 60 to 65 years of age, the higher daunorubicin dose was associated with a benefit in both CR rates (73% vs 51%, respectively) and OS (38% vs 23%, respectively). As with the ECOG study in younger patients, the benefit of higher-dose daunorubicin was seen mostly in those with favorable- or intermediate-risk cytogenetics. The control arm in both of these trials used a relatively low dose of daunorubicin. The Japanese AML Study Group recently asked if in patients younger than 65 years daunorubicin at 50 mg/m² for 5 days was superior to a standard dose of idarubicin (at 12 mg/m² for 3 days), both given with standard cytarabine.[20] The two appeared to be equally effective, with outcomes in the same range as those seen with 90 mg/m² of daunorubicin. These studies suggest that for patients with high-risk AML who are fit enough to undergo intensive chemotherapy, there is no advantage for one or the other anthracycline as long as they are used at appropriate doses. Investigations have also addressed the most appropriate dose of cytarabine for induction. The HOVON group recently published the results of a prospective randomized trial of idarubicin plus cytarabine at either a standard dose (200 mg/m² by continuous infusion on days 1 to 7) or at a higher dose (1000 mg/m² BID on days 1 to 5).[21] Overall, there was no apparent advantage for the escalated dose of cytarabine. However, in an analysis looking for possible effects of the higher dosing in subgroups of patients, there did appear to be a benefit for the higher-dose regimen in patients with a monosomal karyotype; in these patients, the 5-year event-free survival (EFS) and OS were greater with the higher-dose regimen (13% vs 0% for EFS, and 16% vs 0% for OS). Multiple studies have addressed the possibility of adding a third drug to the standard daunorubicin/cytarabine combination. Studies adding etoposide, thioguanine, cladribine, or lomustine have given equivocal results. More recently, several studies have suggested that the anti-CD33 drug conjugate, gemtuzumab ozogamicin, improves results when added to conventional chemotherapy.[22] However, the benefit of gemtuzumab appears limited to patients with intermediate- or favorable-risk cytogenetics. This finding may reflect differences in the nature of the leukemic stem cell according to disease risk, the hypothesis being that good-risk and intermediate-risk disease is associated with a more mature leukemia stem cell that expresses the differentiation antigen CD33, whereas unfavorable-risk AML is associated with very immature stem cells lacking CD33 expression.[23]

**Post-induction therapy**

**Hematopoietic cell transplantation.** Multiple prospective studies have been conducted in which younger AML patients, generally those under age 55, who have achieved a complete remission are assigned to treatment with allogeneic HCT if they have a matched sibling or to aggressive chemotherapy if they lack a donor. Several meta-analyses conducted on such studies show that survival is improved with allogeneic transplant in first remission.[24,25] When examined by cytogenetic risk category, the survival advantage is lost for patients with favorable-risk disease, and is most marked for patients with unfavorable-risk disease. Only about a third of all patients will have a matched sibling to serve as a donor. With the development of unrelated donor registries, it is now possible to find a matched unrelated donor (URD) for many patients. Data from single centers, and more recently from transplant registries, show that the outcomes of transplants from matched siblings and matched URDs are very
similar.[26,27] For example, in a study from the Center for International Blood and Marrow Transplant Research (CIBMTR), transplantation for high-risk AML in 226 recipients of matched related HCT was compared with that in 358 recipients of matched URD HCT. At 3 years, OS was 45% for matched related donors vs 37% for matched URDs. In a multivariate analysis, these outcomes were indistinguishable (relative risk [RR] = 1.06). While matched URDs can be found for many patients, for others no such donors are available. This is a particular problem for blacks, Hispanics, and patients of mixed racial background. In the study from the CIBMTR, outcomes were significantly worse with the use of partially matched URDs. Recently, the results of transplantation from matched related donors, matched URDs, and partially matched double-unit umbilical cord blood transplants were compared in a study from Seattle and Minnesota.[28] Although transplant-related mortality was higher with double cord-blood transplants, relapse rates were lower, leading to equivalent OS with the use of matched siblings, matched URDs, or double cord-blood transplants.

The CIBMTR and Seattle/Minnesota studies suggest that if a matched related donor is not available for a younger patient with unfavorable-risk AML, consideration should be given to proceeding to either a matched unrelated or cord blood transplant. However, it should be emphasized that these were retrospective studies and that considerable patient selection bias could have influenced results. Recently, the results of AMLHD98A from the German-Austrian group were published.[29] In this study, 844 patients were enrolled and 267 were determined to be high risk either by virtue of having high-risk cytogenetics and achieving a CR (n = 51), or not achieving a CR with initial induction therapy (n = 216). Attempts were made to transplant all high-risk patients and, in fact, 61% were actually transplanted. Among high-risk patients, the 5-year OS rates were 6.5% in those not transplanted vs 25.1% in those receiving a transplant. There was no difference in outcome using matched related and matched unrelated donors. Cord blood was used for only a single patient in this trial. The US Leukemia Intergroup is about to launch a study asking if, with the use of matched related, matched unrelated, and cord-blood donors, it is possible to perform transplants on more than 60% of patients with high-risk AML who achieve a first CR.

The role of transplantation for fit but older patients is less clear. There have been essentially no sufficiently sized prospective trials yet reported in which patients have been followed from diagnosis and the outcomes of transplantation vs chemotherapy have been compared. The largest retrospective trial is one from the Japanese National Cancer Center, in which investigators examined the outcome of 1036 AML patients 50 to 70 years of age who achieved a first CR and were treated with either allogeneic HCT (n = 152) or chemotherapy (n = 884).[30] Both OS and relapse-free survival were significantly improved in the HCT group. In patients with unfavorable-risk disease, the 3-year OS with transplantation was 47%, which was not statistically significantly superior to the 35% seen with chemotherapy (P = .20).

Patients with a monosomal karyotype have an extremely poor prognosis if they are treated with conventional chemotherapy. Whether allogeneic HCT can improve upon this has been addressed in several retrospective studies. We examined our results in Seattle and found that the 4-year OS after allogeneic HCT was 52% for patients who had poor-risk cytogenetics without a monosomal karyotype, and 28% for those with a monosomal karyotype.[31] While the presence of a monosomal karyotype predicts for a poorer outcome after allogeneic HCT, the outcome with transplant is still considerably better than might be expected with standard chemotherapy. In the Seattle study, there was no difference in outcome using matched related or matched URDs. The German-Austrian Group has also since examined outcomes of allogeneic HCT for patients with a monosomal karyotype. In their experience they found a 4-year survival of 50% for recipients of matched related transplants performed in CR1, but only 15% with matched URDs.[32] The reasons for the high rates of failure in recipients of URDs in the German experience were not detailed.

Chemotherapy. If younger patients with unfavorable cytogenetics are not transplanted in first remission, some form of consolidation therapy is needed, but the best form is less certain. The Japanese Adult Leukemia Study Group recently published a comparison of 3 courses of high-dose cytarabine (2 g/m2 BID for 5 days) vs 4 cycles of conventional-dose multi-agent therapy as consolidation therapy for patients.[33] While the high-dose cytarabine arm led to superior disease-free survival and OS in patients with favorable-risk disease, it had no advantage for patients with intermediate- or unfavorable-risk cytogenetics. Similarly, a recent German trial compared intermediate-dose vs high-dose cytarabine, both combined with mitoxantrone, as consolidation for patients with intermediate- or unfavorable-risk AML.[34] They found no advantage to the higher-dose regimen.

Treatment of patients who are not candidates for intensive therapy
The definition of who is “not a candidate for intensive therapy” is influenced by many factors. The patient’s own perspective, of course, plays a central role, with some patients placing a higher premium on short-term quality of life than others. The objective risk of immediate mortality, as measured for example in the multi-component model we have recently published, plays a major role in the definition.[16] In addition, the anticipated outcome of therapy enters into the discussion—if the likelihood of complete response and long-term survival with intensive therapy is high, then one might broaden the definition of who is eligible, but if the benefits of intensive therapy are marginal, then exposing less healthy patients to that therapy might not be in their best interests.

If the choice is made to not pursue aggressive treatment, then the proven therapeuic options for patients with unfavorable-risk AML are limited. Palliative care alone may be an appropriate choice for patients with substantial comorbidities. In a randomized trial not limited to patients with unfavorable-risk cytogenetics, low-dose cytarabine was found to be superior to hydroxyurea.[35] Single-agent clofarabine (Clolar), studied in a cohort of 112 patients older than age 60, resulted in an encouraging CR rate of 42% in patients with unfavorable risk cytogenetics.[36] Azacitidine (Vidaza) and decitabine (Dacogen) have both been found to have activity in this population of patients.[37,38] In an interesting recently published trial, Fenaux et al asked physicians to select one of three approaches as their “standard therapy”—supportive care alone, low-dose cytarabine, or standard daunorubicin plus cytarabine—and then randomized 113 patients to either the selected standard care or to azacitidine.[39] Median OS for the azacitidine group was 24.5 months compared with 16 months in the conventional treatment group. In the small subset of patients with unfavorable-risk cytogenetics (27 total), those treated with azacitidine had a median survival of 12 months compared with 5 months in those treated with conventional care. The longer survival did not depend on achieving a CR. Current trials are addressing whether the addition of agents such as vorinostat (Zolinza) or lenolidomide (Revlimid) to azacitidine will increase antitumor activity.[40]

Summary

Although the overall prognosis for patients with AML associated with unfavorable, complex, or monosomal karyotypes is poor, some patients can be cured. The best chance for cure is seen in patients who achieve a CR with induction therapy and proceed to allogeneic transplantation. There is some suggestive but not strong evidence that inclusion of high-dose cytarabine during induction might be of some benefit for this difficult subgroup. Improved outcomes with matched unrelated and double cord-blood transplantation mean that donors can now be found for most patients in need. For patients who are not candidates for aggressive therapy, preliminary data suggest that outcomes which are at least equivalent, if not superior, to those achieved with aggressive treatment can be obtained using azacitidine or decitabine instead of standard induction therapy. The generally poor outcomes with all commercially available forms of therapy for unfavorable-risk AML argue strongly for considering entry of these patients into clinical trials.

Financial Disclosure: The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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