Abstract

Acute myelogenous leukemia (AML), although a relatively rare cancer, is the most common form of acute leukemia to occur in adults. The diagnosis and treatment of patients with AML has traditionally been based on cytogenetic prognostic markers. However, significant advancements in the discovery of the numerous molecular, cytogenetic, and biologic factors affecting this disease have revealed clear patient subgroups who respond uniquely to therapy. Achieving the best response to current and emerging therapies is dependent on understanding how each of these patient subgroups responds to each intervention. This monograph details the current and emerging treatment strategies available for adult patients with AML. Included are discussions of specific patient subgroups, as well as novel therapeutic agents under investigation in this disease.
Target Audience: This activity has been designed to meet the educational needs of oncologists, hematologist/oncologists, hematologists, and oncology nurses involved in the management of patients with acute myeloid leukemia (AML).

Statement of Need/Program Overview: Several new prognostic factors have been identified in AML, leading to greater specificity of subgroups, prognosis, and treatment options. In addition, many new drugs are being evaluated for the treatment of AML. These emerging data may not be fully understood by practicing hematologists/oncologists in the community setting. A Clinical Roundtable Monograph is the ideal vehicle through which community-based physicians can learn about these recent advances.

Educational Objectives
After completing this activity, the participant should be better able to:
- Describe the importance of existing and emerging agents in the natural history of AML.
- Review results of clinical trials evaluating new treatment options in AML.
- Identify future research directions for the treatment of AML.

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Media: Monograph

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Incorporating Novel Treatment Strategies Into Conventional Therapy

Elihu H. Estey, MD

**Conventional Treatment for Adult AML**

The combination of an anthracycline and cytarabine (ara-C) has been considered standard therapy for the induction of remission of adult AML for nearly 4 decades. This combination, referred to as the ‘3+7 regimen’, consists of an anthracycline (eg, idarubicin or daunorubicin) administered daily for 3 days, followed by 7 days of a continual cytarabine infusion (100–200 mg/m²).

The patient’s bone marrow is assessed approximately 2–3 weeks after receiving treatment. In the event that the marrow continues to show blasts, the patient typically receives a second course of the same drugs, generally given at a reduced dosage (ie, 2+5 regimen). Conversely, if the bone marrow is hypoplastic, a second course of therapy is delayed until evidence of AML disease reemergence.

Little change in AML patient survival has been reported over the past several decades. However, there are 3 patient subgroups which are notable exceptions to this—all in younger patients (<60 years) with specific subtypes of AML. The first of these groups consists of patients with acute promyelocytic leukemia (APL), whose rates of complete response (CR) improved to 90%, and cure rates have approached 85% with the addition of new treatments including all-trans retinoic acid (ATRA) and arsenic trioxide. The unique sensitivity of APL to ATRA differentiates it from other subtypes of AML, and due to its high cure rate, APL is often now not included as an AML subtype. The second group of patients experiencing significant improvements in survival includes those with core binding factor (CBF) AML. CBF AML is characterized by cytogenetic abnormalities that result in the disruption of genes that encode subunits of the CBF, a transcription factor important for the normal regulation of hematopoiesis. These abnormalities include translocation t(8;21)(q22;q22) or inversion of chromosome 16 [inv(16)(q13;q22)/t(16;16)(p13;q22)], and are associated with a more favorable prognosis. CBF AML displays a particular sensitivity to high-dose cytarabine (1–3 g/m² per dose), which induces a CR in more than 90% of patients.

The monoclonal antibody gemtuzumab ozogamicin has also contributed to the improved patient survival in CBF AML patients. The third group of patients who have experienced significant improvements in survival are those with an abnormal karyotype. Although these patients respond to high-dose cytarabine, they do not do so to the same extent as do CBF AML patients, and therefore do not achieve as great a survival advantage as CBF AML patients.

In general, prognostic factors reveal more about what therapies a patient should not receive as opposed to which ones they should. Unfortunately, most patients still receive the standard 3+7 regimen, despite the fact that many patients will not respond well to therapy. Historically, the principal predictor of patient response to therapy was whether the patient had primary or secondary AML. Cytogenetics have also frequently been used as a prognostic factor, although in the past 5–10 years, there has been a greater push for more molecularly-based markers such as the FMS-like tyrosine kinase 3 (FLT-3). Indeed, incorporating these molecular markers when categorizing patients reveals much more prognostic information than cytogenetics alone. Age behaves as a continuous variable in AML patients. For example, there is more of a prognostic difference between 2 older patients ages 61 and 68 years than between a patient who is 58 and one who is 61 years. Other factors can modify the effect of age, and a patient between 60–69 years with a performance score (PS) lower than 2 and normal cytogenetics has a better prognosis compared with a patient between 50–59 years with a PS of 2 and poor cytogenetics. However, despite the fact that age is the most simple and common division when categorizing AML patients, the most important factor for predicting treatment-related death is performance status.

**Determining the Efficacy of Emerging Therapies**

Novel agents for AML are generally reserved for use in patients who are either older or have experienced a disease relapse. Many agents have been investigated in the clinical setting in these patient populations, including clofarabine, cloretazine, decitabine, and azacitidine. Overall, these agents are associated with a lower rate of early death (within 30 days). This decreased rate of early death is likely due to reduced organ
It is generally accepted that future treatment strategies for AML patients lie in effective combination regimens. Therefore, instead of evaluating if a novel agent is more effective than a standard 3+7 regimen, the real question is: can that novel agent be improved upon itself?

This question was recently investigated in a randomized trial comparing clofarabine versus clofarabine plus low-dose cytarabine as frontline therapy for older AML patients. A significantly higher CR rate was observed with the combination versus the single-agent therapy (63% vs 31%, \( P=0.025 \)). Although event-free survival (EFS) was also significantly improved with the combination therapy (7.1 vs 1.7 months, \( P=0.04 \)), the improvement in OS was not determined to be of statistical significance (11.4 vs 5.8 months, \( P=NS \)) (Figure 1).

A pilot combination study evaluated azacitidine plus gemtuzumab ozogamicin, finding this combination safe and effective in elderly AML patients. A CR was achieved in 55% of patients, and the median OS was 10 months. Notably, this was a higher CR than achieved with gemtuzumab ozogamicin alone (22%) or azacitidine alone (18%) in similar patient populations.

Other combination strategies include combining the hypomethylating agent decitabine with valproic acid (VPA), although a phase I study showed a higher risk of encephalopathy associated with this combination. Vorinostat, a histone deacetylase (HDAC) inhibitor, is also under investigation in combination with gemtuzumab ozogamicin, either with or with azacitidine. These and many other combination strategies are currently being evaluated in AML patients.

An important point to make regarding the investigation of novel and combination therapies is that the phase III trial is becoming no longer useful in the setting of AML. Phase III trials take too long to complete and are largely limited by 2 treatment arms—an investigational and a conventional (control) treatment. In addition, due to the very small differences or improvements which are generally observed, a large number of patients are needed to complete the trial in order to determine statistical significance. With advancements in cytogenetics and genetic mutations in AML, it has also become increasingly clear.

### Table 1. Early Death Versus Resistance as Cause of Failure With 3+7 Regimen

<table>
<thead>
<tr>
<th>Age</th>
<th>56–65</th>
<th>66–75</th>
<th>&gt;75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>246</td>
<td>274</td>
<td>80</td>
</tr>
<tr>
<td>CR</td>
<td>46%</td>
<td>39%</td>
<td>33%</td>
</tr>
<tr>
<td>Early death</td>
<td>11%</td>
<td>20%</td>
<td>31%</td>
</tr>
<tr>
<td>Resistance</td>
<td>43%</td>
<td>41%</td>
<td>36%</td>
</tr>
</tbody>
</table>


CR=complete response

toxicity, such as that in the gut or the lung. Like conventional chemotherapy, these drugs result in significant myelosuppression; however, unlike patients who experience organ failure, many patients with myelosuppression can go on to live for several months. This is in contrast to the typical 3+7 chemotherapeutic regimen, which can result in early death, most often due to organ failure in addition to myelosuppression.

However, a retrospective analysis of 968 adults with AML from 5 SWOG trials demonstrated that the real issue in the treatment of older AML patients receiving a standard 3+7 regimen is not early death, but resistance. In this study, although patients aged 66–75 years achieved a 39% rate of CR, they experienced a 41% rate of therapy resistance compared with only a 20% rate of early death. Similarly, patients who were 75 years or older achieved a 33% rate of CR, had a 31% rate of early death, and a 36% rate of resistance (Table 1). These data suggest that the major problem with a standard 3+7 regimen is not toxicity resulting in early death, but a lack of response. Therefore, the real question to be determined with novel agents is not if these agents can reduce the risk of early death—although many can—but if the therapy can be more effective than conventional treatment. Unfortunately, this is a major problem in the investigation of emerging therapies for AML. Currently, there is little evidence to show whether they are indeed more effective than standard therapy. In addition, it is important to consider that even if an agent might increase a patient’s overall survival (OS) by 6 months, it may still be more beneficial for that patient to instead enroll in a clinical trial.

One recently published phase III study compared azacitidine with conventional care in patients with high-risk myelodysplastic syndrome (MDS), although when the patients were reviewed, it was found that 32% were found to have AML. These patients were randomized to receive either azacitidine or conventional care regimens, consisting of a 3+7 intensive chemotherapy regimen, low-dose cytarabine, or best supportive care. Azacitidine improved median OS compared with conventional care (24.5 vs 15.0 months,

hazard ratio [HR] 0.58, \( P<.0001 \)), as well as the 2-year OS (50.8% vs 26.2%, \( P<.0001 \)).

It is important to note that the primary mechanism of action of many of these novel agents in AML has not yet been established. For example, even if decitabine is known to be a hypomethylating agent, it is not known for sure if its activity in AML is due to this specific activity, or the result of another effect.

### Combination Strategies for AML Patients

It is generally accepted that future treatment strategies for AML patients lie in effective combination regimens. Therefore, instead of evaluating if a novel agent is more effective than a standard 3+7 regimen, the real question is: can that novel agent be improved upon itself?
that it is unreasonable to think that all of the patients recruited to these trials are inherently similar, and thus should not be treated as such. When determining efficacy or activity, it is important to consider that often, ‘improvements’ observed within these trials are largely insignificant to the patient (i.e., an improvement in survival of at most 6 months). These trials are powered in such a way that there is greater concern for false positives than false negatives. While the issue of a false positive is important when the standard therapy is already very good, this is not the case in AML. Therefore, to improve these trials, it is necessary to aim for larger improvements in response, using a lower statistically significant threshold (i.e., P = .10). Consequently, these changes would allow for smaller, quicker phase III AML trials, and permit more therapies to be investigated in this setting.

References


Figure 1. Survival and event-free survival rates: clofarabine versus clofarabine plus low-dose cytarabine.


LDAC = low-dose cytarabine


19. Fenaux P, Mufti GJ, Hellström-Lindberg E, et al. Azacitidine prolongs overall survival (OS) and reduces infections and hospitalizations in patients (pts) with WHO-defined acute myeloid leukemia (AML) compared with conventional care regimens (CCR) program and abstracts of the 50th American Society of Hematology annual meeting and exposition; December 6-9, 2008; San Francisco, California: Abstract 3636.

Clinical Trials in Adult AML

Wendy Stock, MD

Incorporating a Targeted Agent into Frontline Therapy

Recent insights into the molecular pathogenesis of AML have suggested that this disease may be effectively treated with targeted therapies. Several clinical trials are now exploring the addition of a targeted agent to frontline therapy for AML.

One of the largest and most international clinical trials currently ongoing in AML is the Cancer and Leukemia Group B (CALGB) 10603 study. This is a phase III randomized, double-blind study evaluating the addition of the protein kinase inhibitor midostaurin (PKC412) to standard induction and consolidation treatment. Although midostaurin targets multiple protein kinases, it potently inhibits FLT-3, a tyrosine kinase mutated in nearly one-third of patients with AML. Because these patients generally have a poor outcome with current standard approaches, there is much interest in determining if targeting FLT-3 early in therapy could impact the natural history of AML. Preclinical studies have demonstrated that midostaurin is active in AML cell lines with mutated FLT-3. In CALGB 10603, adult patients (<60 years old) with newly diagnosed AML and a confirmed FLT-3 mutation are randomized to 2 arms, receiving either midostaurin or placebo in addition to standard therapy. Remission induction therapy is comprised of the 3+7 regimen daunorubicin (days 1–3) plus continuous cytarabine (days 1–7), and either midostaurin or placebo (days 8–21). At least 4 weeks following induction therapy, those patients with a CR continue on to receive consolidation therapy comprised of high-dose cytarabine (days 1, 3, and 5 every 12 hours) plus midostaurin (days 8–21, twice daily). Consolidation therapy then continues for up to 4 cycles, every 4 weeks. At least 2 weeks following consolidation therapy, patients remaining with a CR receive up to 12 months of maintenance therapy which is comprised of either midostaurin or placebo twice daily. Since there are some data suggesting that patients with FLT-3 mutations may benefit from an allogeneic stem cell transplant in first remission, patients and investigators may choose this approach and they would then continue to be followed for survival. Interim results of this trial have not yet been reported since the study is still in the first year of accrual.

As described in Dr. Estey’s previous section, CBF AML is characterized by translocation \([t(8;21)(q22;q22)]\) or inversion \([\text{inv}(16)(p13q22)/t(16;16)(p13;q22)]\) cytogenetic abnormalities that result in the disruption of genes encoding subunits of the CBF. Patients with CBF AML have a relatively favorable prognosis due to their sensitivity to high-dose cytarabine as frontline consolidation therapy. However, despite these favorable cytogenetics, many patients experience a disease relapse; the cure rate among patients with CBF AML is only 50–60%. Secondary mutations have been identified in a number of patients with CBF AML. Mutations in the receptor tyrosine kinase c-Kit have been identified in 12–47% of patients with \(t(8;21)\) and 22–38% of patients with \(\text{inv}(16)/t(16;16)\), and have been associated with an increased rate of relapse among patients with CBF AML. Importantly, this same study also showed that CBF AML patients with mutated c-Kit had a significantly lower OS (25% vs 76.6%, \(P=.006\)). Recently, 2 larger studies confirmed that CBF AML patients with mutated c-Kit had a significantly higher risk of relapse among patients with CBF AML. In one study, mutations in c-Kit were significantly associated with a shorter EFS and relapse-free survival (RFS). Another report showed a significantly higher incidence of relapse at 24 months among CBF AML patients with c-Kit mutations compared with those without the mutation (90% vs 35.3%, \(P=.006\)). This has provided rationale for targeting c-Kit in these patients with the tyrosine kinase inhibitor dasatinib. An upcoming open label phase I/II clinical trial will evaluate the addition of dasatinib to standard induction, consolidation, and maintenance cycles in patients with CBF AML. This trial is expected to begin in the next few months.

Treatment of Elderly AML Patients

One of the greatest challenges in AML therapy today lies in the treatment of older adults with AML. These patients are typically defined in the AML literature as patients 60 years or older. Generally, older AML patients achieve lower rates of CR and RFS compared with their younger counterparts—an effect which seems to worsen with increasing age. For example, the Medical Research Council (MRC) 8th AML trial comparing the same therapy in younger and older AML patients reported a 70% CR in patients 50 years of age or
younger, compared with a CR rate of 52% for patients 60–69 years of age, and 26% for patients over 70 years of age. A similar trend was noted in the CALGB 8525 study, which also demonstrated a higher CR rate (73% vs 47%) and 4-year disease-free survival (DFS) rate (31% vs 14%) among younger (<60 years) patients versus older patients (≥60 years), respectively. More recently, a retrospective analysis of 5 SWOG trials reported that older AML patients were more likely to present with poor performance status and lower white blood cell counts. Furthermore, this same analysis showed that compared with patients younger than 56 years of age, those who where older than 75 years had a higher incidence of multidrug resistance (33% vs 57%) and unfavorable cytogenetics (35% vs 51%). The CR rate, determined to be less than 50% among patients older than 55 years, was shown to decrease with advancing age. These poor performance characteristics among older AML patients are likely attributed to numerous biologic factors, such as a higher likelihood of progressing to MDS, an increased cellular resistance to chemotherapy, and a higher frequency of karyotypes associated with a poor prognosis. Additionally, features which naturally occur more frequently among the elderly, such as comorbidities and impaired organ function, may further contribute to a reduced response and survival.

A standard 3+7 chemotherapy regimen has been used to treat older AML patients since a 1989 study showed it to be an effective therapy in this patient population. However, the use of high-dose cytarabine consolidation therapy is more controversial among elderly patients, which was found to result in an inferior response in the CALGB 8252 trial, likely due to poor tolerance of the regimen. Therefore, older adults with AML may be the ideal group of patients for clinical trials testing novel and emerging treatment strategies.

One possibility for this high risk subset is testing the feasibility and efficacy of reduced intensity conditioning regimens with allogeneic SCT as frontline therapy. Recent data demonstrate that these regimens are now being used with increasing ease in older AML patients with a reasonable performance status. For example, in a phase II trial of 19 older adults with AML (median age, 64 years) who received a reduced intensity conditioning regimen prior to allogeneic SCT, a 68% rate of 1-year survival was reported. In this trial, the reduced intensity conditioning regimen consisted of fludarabine, melphalan, and carmustine. A separate retrospective study also suggested that a reduced intensity conditioning regimen was as effective as the more myeloablative strategies typically used.

Targeted agents are another treatment option being explored in older adults with AML. One of these is the proteasome inhibitor bortezomib. Bortezomib inhibits cell proliferation and induces cell death by inhibiting protein turnover. Bortezomib was evaluated in older adults with AML in a phase I dose-escalation trial, in which it was combined with idarubicin and cytarabine (administered in a typical 3+7 regimen) as frontline therapy. Of the 31 patients evaluated in this trial, 9 had relapsed AML. Overall, a 61% rate of CR was achieved, with an additional 3 patients achieving a CR with incomplete platelet recovery. Although all doses used in this study were found to be tolerable, a dose of 1.5 mg/m² was selected for future phase II trials of bortezomib in this setting. Based on these promising results, a phase II CALGB trial has been initiated to continue to evaluate bortezomib in this patient population. In this single-arm trial, older patients (60–75 years) will receive bortezomib in addition to daunorubicin plus cytarabine as frontline induction therapy. The primary study outcome will be the rate of remission induced by this therapy.

Several other therapeutic agents have also been investigated for a potential role in the treatment of elderly AML patients. One of these, clofarabine, is a purine analog that induces cell death through inhibition of DNA synthesis. BIOV-121, a phase II study of clofarabine as frontline monotherapy, demonstrated it to be active in AML patients 65 years of age or older, producing a 44% overall response rate (CR and incomplete CR [CRI]) At the American Society of Hematology (ASH) 2008 annual meeting, single-agent clofarabine was also evaluated as frontline therapy in the CLO24300606/CLASSIC II study, a prospective single-arm phase II trial of AML patients 60 years of age or older. Notably, these patients exhibited poor performance status and an unfavorable blast karyotype. A 38% rate of CR was reported in this study, and although a number of patients experienced hepatotoxicity and hematologic toxicities, only 6.2% of patients discontinued therapy due to adverse events. Another agent, the nucleoside analog decitabine, was also evaluated as frontline therapy for older adults with AML in a phase II trial presented at ASH 2008. An overall response of 25% was experienced, and complete remissions were reported in all patient subsets.

References

27. Bortezomib, daunorubicin, and cytarabine in treating older patients with previously untreated acute myeloid leukemia. wwwclinicaltrialsgov: Identifier NCT00742625.
Molecular Characteristics Driving Therapy in AML

Jerald P. Radich, MD

The CALGB 8461 study prospectively analyzed 1,213 adult patients with newly diagnosed AML to determine the effect of certain cytogenetic abnormalities on patient prognosis, including the rate of CR, cumulative incidence of relapse (CIR), and OS.1 All patients received similar treatment consisting of a 3+7 induction regimen, followed by chemotherapy-based consolidation treatment with or without maintenance therapy. Using patient pretreatment karyotypes, the CALGB 8461 study developed a new schema to risk prioritize patients based on the probability of achieving a CR, CIR, and OS. In this schema, patients with a normal karyotype were categorized as intermediate risk. Also included in the intermediate risk category were patients with a t(9;11). Patients with either t(8;21) or inv(16)/t(16;16) were categorized as having a favorable risk. All other patients with either a complex karyotype (≥3 cytogenetic abnormalities) or del 5q, del 7q, or -7 were categorized as having adverse risk. Using this criteria, the rates of CR following induction therapy were 88%, 67%, and 32% for favorable, intermediate, and adverse risk groups, respectively. The estimated 5-year CIR was 0.51 (SE, 0.04), 0.67 (SE, 0.02), and 0.92 (SE, 0.04). The estimated 5-year OS was 55% (95% confidence interval [CI], 47–62%), 24% (95% CI, 21–27%), and 5% (95% CI, 3-8%). (Figure 2).

In recent years, it has become well established that the prognostic impact of cytogenetic abnormalities is greatly influenced by the presence or absence of certain genetic mutations. Overall, the frequency of genetic mutations is high among AML patients (76.4%), and only 23.6% display wild-type genetics.2 However, the availability for testing each genetic mutation is limited. Monitoring AML patients in minimal residual disease (MRD) by either polymerase chain reaction (PCR) or fluorocytometry will become increasingly more common in the near future as more genetic markers become available to help categorize patients into prognostic subgroups. Several lines of data show that patients who are in CR after induction and consolidation therapy and have evidence of MRD by PCR or fluorocytometry have a higher risk of relapse.3,4 This suggests that future clinical trials are needed to determine if modifying therapy based on MRD status is warranted in these patients.

**Case 1: AML Patient (<60 Years) Refractory to Induction Therapy**

Approximately 30% of AML patients do not achieve a remission in response to a standard 3+7 chemotherapy regimen.5 Regardless of their genetic abnormality, these refractory AML patients generally have a poor outcome. Although some of these patients may respond to a salvage regimen that is comprised of high-dose cytarabine, few patients experience a cure.6 Therefore, these patients require an alternative treatment strategy. One possibility is allogeneic SCT.7 A retrospective review of 68 patients who underwent allogeneic SCT for primary refractory AML found the 3-year DFS and OS were 31% (95% CI, 20–42%) and 30% (95% CI, 18–41%), respectively. This same study found that using an unrelated donor as the source of stem cells was significantly associated with shortened OS (relative risk [RR], 2.23; P=.0005) and shortened DFS (RR, 2.05; P=.0014). Unfavorable cytogenetics prior to allogeneic SCT was also significantly associated with shortened OS (RR, 1.68; P=.0107) and shortened DFS (RR, 1.58; P=.0038).

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Case 2: AML Patient (<60 Years) With Good Risk Cytogenetics

The majority of AML patients with favorable cytogenetics are classified as having CBF AML, described in the earlier portions of this roundtable. An analysis of 370 patients (ages 16–83 years) with newly diagnosed CBF AML showed that 87% achieved a CR. DFS was not significantly affected by the type of cytogenetic abnormality experienced by the CBF AML patients; in fact, it was similar between patients with either inv(16) or t(8;21). When the 5-year DFS was further analyzed, researchers found that it was greatly impacted by the type of post-remission therapy that the patient had received. Although the 5-year DFS was relatively similar among patients who received fludarabine plus cytarabine, SCT, or high-dose cytarabine (61%, 61%, and 50%, respectively), patients who received other therapies had a much lower 5-year DFS (31%). The superiority of FA, HCT, and HDAC therapy remained, even after adjusting for patient age and percentage of peripheral blasts.

The prognosis of CBF AML patients can be further subcategorized using other genetic lesions. For example, c-Kit mutations are a common mutation among AML patients. In an analysis of 1,940 randomly selected AML patients, c-Kit mutations were significantly more common among those patients with a t(8;21). Among t(8;21) patients, those with c-Kit mutations had a significantly lower median OS compared with those without a c-Kit mutation (304 vs 1,836 days, respectively; \( P = .006 \)). A similar trend was observed with median EFS as well (244 vs 744 days, respectively; \( P = .003 \)). Another study of 61 patients with inv(16) and 49 patients with t(8;21) also evaluated the relationship between these cytogenetic abnormalities and c-Kit mutations. A 5-year CIR was significantly higher in inv(16) patients positive for mutated c-Kit compared with those negative for mutated c-Kit (56% vs 29%, \( P = .05 \)). Similar results were also observed for t(8;21) patients (70% vs 36%, \( P = .017 \)). Mutated c-Kit predicted a poorer OS among inv(16) patients but not t(8;21) patients. Therefore, even patients with a favorable cytogenetic prognosis may be further subdivided, and thus affect treatment options.

Case 3: AML Patient (<60 Years) With Intermediate Risk Cytogenetics

The majority of patients categorized as intermediate risk have normal cytogenetics, although this category also includes patients with +8, +6, or –y. Importantly, a number of these cytogenetically normal patients do display genetic mutations. A recent study investigated the mutational status of 872 cytogenetically normal adult AML patients (<60 years of age) and correlated their mutational status with clinical outcome. One of the most common mutations found was in the nucleophosmin gene (NPM1), occurring in 53% of patients. NPM1 mutations are associated with a favorable prognosis and improved survival. Another highly mutated gene (42%) was found to be FLT-3 (31% occurring as internal tandem duplications [ITD] and 11% as mutations within the tyrosine kinase domain [TKD]). FLT-3 ITD is linked with a decreased duration of remission and reduced OS; conversely FLT-3 TKD mutations are associated with improved survival. The CCAAT/ enhancer binding protein alpha gene (CEBPA) was found to be mutated in 13% of the study population; mutations in CEBPA are associated with increased remission duration, OS, and DFS. Finally, 7% of the study population exhibited partial tandem duplications (PTD) in the mixed-lineage leukemia gene (MLL). MLL PTD has been linked with a decreased duration of remission. These genetic mutations may be compiled together to help form a patient’s prognosis. For example, NPM1 mutations and FLT-3-ITD have been shown to significantly interact with each other in younger adults with AML. Patients positive for an NPM1 mutation and who are FLT-3 ITD-negative have a significantly superior prognosis, with the highest rates of OS and RFS compared with other NPM1/FLT-3 combinations (Figure 3). In fact, modern SCT strategies are quite effective in patients with intermediate risk disease, as it is with poor risk disease. A meta-analysis of 1,151 AML patients found that allogeneic SCT after first CR offered a significant advantage in OS (HR, 1.15; 95% CI, 1.01–1.32; \( P = .037 \)). Further, this analysis showed that the efficacy of allogeneic SCT was dependent on the cytogenetic risk of the patient. Allogeneic SCT was especially effective in patients with poor risk (HR, 1.39) and intermediate risk (HR, 1.24) cytogenetics, but was less effective in patients with good risk (HR, 0.90).

Case 4: AML Patient (<60 Years) With Poor Risk Cytogenetics

Poor risk AML patients have del 5q, del 7q, +7, or complex cytogenetics, defined as 3 or more cytogenetic abnormalities. These patients typically have poor outcomes to conventional therapy, and should be considered for secondary therapeutic strategies or SCT. The results of SCT in this patient subgroup differ depending on the study, but in general, approximately 30–40% of patients with poor risk cytogenetics can be cured with this strategy.
Older patients (≥60 years of age) in general have a poorer prognosis and decreased response to therapy, partly due to a higher frequency of high-risk cytogenetics. Only 5–10% of older AML patients are cured with conventional therapy, and there is no difference depending on the type of induction regimen. A phase III study of 3 induction regimens (a standard 3+7 regimen composed of 3 days of either daunorubicin, idarubicin, or mitoxantrone with 7 days of cytarabine) in 362 older AML patients showed no difference in OS.17 The CALGB 8641 evaluated the prognostic impact of the cytogenetic profile of 635 older AML patients (≥60 years of age) who were treated with conventional frontline therapy.18 Overall, nearly half of these patients (48.5%) achieved CR, but the 5-year OS rate was 6.6%. Complex cytogenetics (≥3 cytogenetic abnormalities) predicted a lower rate of CR compared with other patients (25% vs 56%). Patients with 5 or more cytogenetic abnormalities performed even worse and had a significantly lower 5-year DFS compared with patients with other karyotypes (0% vs 9.1%, P<.001).

**Figure 3.** Treatment results according to the combined nucleophosmin gene (NPM1) and FLT-3 ITD mutation status. NPM1 predicts favorable prognosis in younger adults with acute myeloid leukemia and normal cytogenetics. Data adapted from Döhner et al. Blood. 2005;106:3740-3746.

**Case 5: AML Patient (≥60 Years)**

Older patients (≥60 years of age) in general have a poorer prognosis and decreased response to therapy, partly due to a higher frequency of high-risk cytogenetics. Only 5–10% of older AML patients are cured with conventional therapy, and there is no difference depending on the type of induction regimen. A phase III study of 3 induction regimens (a standard 3+7 regimen composed of 3 days of either daunorubicin, idarubicin, or mitoxantrone with 7 days of cytarabine) in 362 older AML patients showed no difference in OS.17 The CALGB 8641 evaluated the prognostic impact of the cytogenetic profile of 635 older AML patients (≥60 years of age) who were treated with conventional frontline therapy.18 Overall, nearly half of these patients (48.5%) achieved CR, but the 5-year OS rate was 6.6%. Complex cytogenetics (≥3 cytogenetic abnormalities) predicted a lower rate of CR compared with other patients (25% vs 56%). Patients with 5 or more cytogenetic abnormalities performed even worse and had a significantly lower 5-year DFS compared with patients with other karyotypes (0% vs 9.1%, P<.001).

**References**


Emerging Treatment Options in Adult Acute Myelogenous Leukemia

CME Post-Test: Circle the correct answer for each question below.

1. According to Dr. Estey, all of the following AML patient subgroups have exhibited improved survival in response to treatment, EXCEPT:
   a. Patients <60 years of age with APL
   b. Patients <60 years of age with CBF AML
   c. Patients >60 years of age with CBF AML
   d. Patients <60 years of age with an abnormal karyotype

2. According to Dr. Estey, which of the following prognostic factors is the most important for predicting treatment-related death?
   a. Performance status
   b. Age
   c. Cytogenetics
   d. Molecular genetics

3. Which of the following statements is TRUE regarding a randomized study comparing single-agent clofarabine with clofarabine plus low-dose cytarabine as frontline therapy in older AML patients?
   a. A slightly lower CR was observed with the combination versus the single-agent therapy.
   b. A significantly higher CR was observed with the combination versus the single-agent therapy.
   c. OS was significantly improved in patients who received the combination strategy.
   d. EFS was not significantly improved in patients who received the combination strategy.

4. CALGB 10603, an ongoing study discussed by Dr. Stock, is a phase III randomized trial to determine the efficacy of adding which agent to standard therapy?
   a. Azacitidine
   b. Midostaurin
   c. Dasatinib
   d. Bortezomib

5. In a study discussed by Dr. Stock, CBF AML patients with mutated c-Kit had a significantly lower OS of _________ compared with the OS of 76.6% among CBF AML patients without mutated c-Kit.
   a. 25%
   b. 32%
   c. 38%
   d. 45%

6. In a retrospective analysis of 5 SWOG trials, discussed by Dr. Stock, which of the following was NOT true regarding older (>75 years) AML patients?
   a. Elderly patients had a higher incidence of multidrug resistance.
   b. Elderly patients had a higher incidence of unfavorable cytogenetics.
   c. Elderly patients had a decreasing rate of CR, which continued to decrease with age.
   d. Elderly patients were more likely to present with higher white blood cell counts.

7. BIOV-121, a phase II trial discussed by Dr. Stock, showed that frontline clofarabine monotherapy is active in patients ≥65 years of age, producing what rate of CR + CRI?
   a. 25%
   b. 32%
   c. 44%
   d. 57%

8. In the CALGB 8461 study, what risk category was given to AML patients with a normal karyotype?
   a. Favorable risk
   b. Intermediate risk
   c. Adverse risk

9. A retrospective review, discussed by Dr. Radich, showed that allogeneic SCT was an effective treatment strategy for patients with primary refractory AML. Which of the following is NOT true regarding the findings of this study?
   a. The 3-year OS was 30%.
   b. Having an unrelated donor as the source of stem cells was significantly associated with shortened OS.
   c. Unfavorable cytogenetics prior to allogeneic SCT were significantly associated with shortened DFS.
   d. Poor performance status prior to allogeneic SCT was significantly associated with shortened OS.

10. True or False? Younger patients with NPM1 mutations who are FLT-3 ITD-negative have a significantly superior prognosis compared with other NPM1 and FLT-3 ITD combinations.
    a. True
    b. False
Evaluation Form: Emerging Treatment Options in Adult Acute Myelogenous Leukemia

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
1 = Strongly Disagree    2 = Disagree    3 = Neutral    4 = Agree    5 = Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

1. Describe the importance of existing and emerging agents in the natural history of AML 1 2 3 4 5
2. Review results of clinical trials evaluating new treatment options in AML 1 2 3 4 5
3. Identify future research directions for the treatment of AML 1 2 3 4 5

Overall Effectiveness of the Activity

The content presented:
Was timely and will influence how I practice 1 2 3 4 5
Enhanced my current knowledge base 1 2 3 4 5
Addressed my most pressing questions 1 2 3 4 5
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Addressed competencies identified by my specialty 1 2 3 4 5
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Name one thing you intend to change in your practice as a result of completing this activity.

Please list any topics you would like to see addressed in future educational activities.

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