AML: Current and Emerging Treatment Approaches

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Abstract

In addition to traditionally recognized prognostic factors, several new cytogenetic factors are now being integrated into the diagnosis and treatment of patients with acute myeloid leukemia. The identification of these molecular markers and their associated prognosis can impact treatment considerations for patients of all ages. Many new therapeutic avenues are currently being explored in clinical studies. Some new agents appear to target specific cytogenetic mutations, such as FLT3; others are being developed without particular cytogenetic subgroups as the main treatment population. Either way, several intriguing new agents are now emerging from clinical studies, and several more are showing promise in phase II and III clinical trials. This monograph includes discussions about the host of recently recognized prognostic factors, new and already existing drugs being evaluated for the treatment of AML, recently completed and ongoing clinical trials, and important directions for future research.

Sponsored through an educational grant from Cephalon, Inc.

Supported by Postgraduate Institute of Medicine.
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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Existing and Emerging Therapeutic Options for The Treatment of Acute Myeloid Leukemia

Martin Tallman, MD

As is the case with many hematologic malignancies, acute myeloid leukemia (AML) is a relatively uncommon disease with approximately 13,400 new cases in the United States per year.1 The median age at the time of diagnosis is approximately 68 years old, and age is an important factor in therapeutic decision-making.

AML can arise de novo, but many patients have therapy-related AML, which evolves from antecedent hematologic disorders such as myelodysplastic syndrome (MDS), or a myeloproliferative disorder.

One of the most important advances in recent years is the appreciation that AML is not a single disease. Rather, it is a heterogeneous group of disorders. Knowing that a patient exhibits a particular chromosomal abnormality is not enough to characterize the patient as belonging to one AML subtype or another, even within specific genetic subtypes: heterogeneity exists beyond the level of cytogenetic grouping.2

For example, AML exhibiting the t(8;21) abnormality was, until recently, considered a single subtype of AML. However, recent research has revealed several subdivisions of t(8;21) AML, each likely associated with its own distinct prognosis. For example, AML patients with t(8;21) have a more favorable prognosis relative to other cytogenetic subtypes, but t(8;21) patients who also have a c-KIT mutation have a very unfavorable prognosis.3

Such findings impact treatment options for t(8;21) patients. Allogeneic transplant has not been commonly pursued for patients with t(8;21) AML, but considering the poor prognosis associated with t(8;21) patients with c-KIT mutation, a matched-sibling transplant, or perhaps even a matched unrelated donor transplant, is a reasonable consideration.3 Such observations reflect the current state of AML research and treatment and represent an important step forward for patients.

Prognostic Factors

Several prognostic factors have been clearly described for AML that, upon analysis, enable clinicians to determine whether a patient has a favorable (approximate 5-year overall survival [OS] of 55%), intermediate (5-year OS of 40%), or poor (5-year OS of 10%) prognosis.4

Age, the intensity of post-remission therapy, and cytogenetics are the most well-studied prognostic factors for AML. It has become routine practice to conduct a chromosome analysis for all newly diagnosed patients because research has clearly shown that cytogenetics are often closely associated with prognosis.

Today, new prognostic factors are emerging in the form of molecular markers. These markers are particularly useful because they tend to occur in patients with so-called normal karyotype AML, which comprises about 40% of all AML patients.5

Normal karyotype AML has generally been considered to have an intermediate prognosis. However, recent findings have demonstrated several identifiable molecular markers within this patient category, including Wilms Tumor 1 (WT1), FLT3, and EVI1, all of which confer an unfavorable prognosis.5-9 Other molecular markers, such as C/EBP-alpha and NPM1, are associated with a very favorable prognosis.10-11

The identification of these molecular markers and their associated prognosis can significantly impact treatment considerations, such as whether or not to offer an allogeneic stem cell transplantation, for such patients. For example, because FLT3-negative patients who are also NPM1-positive are considered to have a relatively favorable prognosis, they would likely not be candidates for a stem cell transplant.

Current Treatment Strategies and Outcomes

The general strategy for AML includes induction therapy and post-remission therapy. Induction therapy usually consists of an anthracycline (typically daunorubicin) and cytarabine, followed by multiple doses of cytarabine with or without transplant for consolidation.

Most clinicians recommend allogeneic transplantation for patients with high-risk disease. This approach would include an allogeneic matched-sibling transplantation if possible, and an alternative donor transplant in the absence of a suitably matched sibling. This option would also be considered for younger, intermediate-risk patients, except for those who are FLT3-negative/NPM1-positive.

For patients under age 60, the complete remission (CR) rate following induction and post-remission consolidation therapies with or without a transplant is very high: approximately 70–80%.12 The early death rate is 5–10%, but OS is only 35–40%, despite the high CR rates.

Outcomes among older patients are poorer. Among this population, the CR rate is 40–50% following induction and
consolidation therapies. The early death rate is approximately 15–20%, and OS is approximately 10–15% at 3–5 years.\textsuperscript{13}

Dose intensification is one area that has been explored in order to improve outcomes. Avenues that have been explored are the inclusion of cytarabine in induction therapy, chemotherapeutic regimens other than daunorubicin plus cytarabine for consolidation therapy, and possible maintenance therapy regimens.\textsuperscript{14,15} However, other than intensifying post-remission cytarabine therapy for younger patients, no dose-intensification strategy has proven effective. Likewise, the addition of etoposide has not led to improvements in outcome, nor has the use of mitoxantrone plus etoposide as induction therapy.\textsuperscript{16,17}

**Emerging Treatments for AML**

There are currently 2 main areas of focus in AML. One area is stem cell transplantation, for which the pool of potential patients has been expanded. Today, patients who were formerly not considered transplant candidates, such as older patients, are being considered for reduced-intensity conditioning transplants.\textsuperscript{18} Other patients are undergoing matched-unrelated donor and umbilical cord donor transplants—2 approaches that were uncommon in the past. The other area is new agents. A number of new compounds that can be directed to specific genetic subtypes of AML are now beginning to be integrated into therapy for AML.

For patients with acute promyelocytic leukemia (APL), treatment with all-trans retinoic acid (ATRA) plus chemotherapy or in combination with arsenic represent significant advances. ATRA and arsenic are novel agents directed against the PML-RAR-alpha fusion transcript. With these new therapeutic options, APL is now the most highly curable subtype of AML, with 80–85% of patients cured of their disease.\textsuperscript{19-21} Outcomes among high-risk APL patients are not as good as those for low- and intermediate-risk patients, due to a higher induction mortality rate and a higher relapse rate.

For patients with CD33-positive AML, the immunon conjugate agent gemtuzumab ozogamicin has been proven advantageous. This drug has been approved by the US Food and Drug Administration (FDA) in this setting, but only for patients over age 60 who are in first relapse.\textsuperscript{22} The remission rate associated with single-agent gemtuzumab for CD33-positive AML patients is 26%.\textsuperscript{23}

Patients with FLT3 mutations can potentially now benefit from newly available FLT3 inhibitors; patients with c-KIT mutations can be treated with tyrosine kinase inhibitors such as dasatinib. Farnesyltransferase inhibitors (FTIs) are proving effective in the treatment of AML patients with ras mutations.\textsuperscript{24}

Combination therapy with these new agents is a very promising approach. Studies have found a very high CR rate in younger patients treated with gemtuzumab plus intensive induction and consolidation chemotherapy.\textsuperscript{25} Following these encouraging data, there are several ongoing randomized trials verifying this approach. Data have begun to emerge from these studies confirming the efficacy of this combination for low- and intermediate-risk patients in extending disease-free and possibly OS.\textsuperscript{26}

As mentioned above, the FLT3 inhibitors are another promising class of agents for the treatment of AML. These agents—CEP701 and PKC412—specifically target the FLT3 mutation and often the c-KIT mutation as well.\textsuperscript{27} These agents may also target the vascular endothelial and platelet-derived growth factors.

Several single-agent studies have shown that CEP701 and PKC412 have some biologic effect on AML such as reducing the blast count, but are not necessarily effective in extending survival time. However, subsequent studies of these FLT3 inhibitors combined with chemotherapy have demonstrated high remission rates.\textsuperscript{28,29} Following these initial findings, an ongoing randomized clinical trial is evaluating daunorubicin plus cytarabine with or without PKC412 in young patients with FLT3 internal tandem duplication. These findings will be discussed in more detail in the following discussions.

Likewise, FTIs appear to be more effective when combined with chemotherapy, rather than given as single agents. These inhibitors—the most well-studied of which is tipifarnib—target ras mutations, which occur in 15–25% of

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**Table 1. Cytogenetic Prognostic Factors in Acute Myeloid Leukemia**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Associated Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(8,21)</td>
<td>Favorable</td>
</tr>
<tr>
<td>t(16,16) (eg, inversion 16)</td>
<td>Favorable</td>
</tr>
<tr>
<td>NPM1</td>
<td>Favorable</td>
</tr>
<tr>
<td>C/EBPa</td>
<td>Favorable</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Trisomy 8</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Complex karyotypes: monosomy 5, monosomy 7, del5, del7, inv(3), t(6,9)</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>11q23</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>WT1</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>FLT3</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>EVI1</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>MLL</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>ERG</td>
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</tr>
<tr>
<td>BAALC</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>BAX</td>
<td>Unfavorable</td>
</tr>
</tbody>
</table>

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4 Clinical Advances in Hematology & Oncology Volume 6, Issue 11, Supplement 18 November 2008
AML patients. These mutations are most common among patients with (3;5) or inv(16) abnormalities. In a large randomized trial evaluating 2 doses and schedules of tipifarnib in previously treated adults aged 70 or older, the remission rate was 5–10%. Investigators are hopeful that combination studies will yield better outcomes.

Clofarabine, a novel purine analog, is another promising agent for AML. Interestingly, this drug appears to have more single-agent activity than some of the others discussed above. In older, previously treated AML patients, single-agent clofarabine is associated with remission rates of 40–60%. In particular, this agent appears to be effective for patients with adverse cytogenetics, with an associated remission rate of approximately 40%.

Amonafide, a topoisomerase II inhibitor, is another potentially interesting agent for AML. This compound intercalates into DNA, disrupts chromatin, and induces apoptosis. This agent may be more effective for therapy-related AML rather than de novo AML. Encouraging phase II data spurred the initiation of an ongoing large randomized trial of amonafide plus cytarabine versus daunorubicin plus cytarabine in therapy-related and secondary AML.

Finally, a new group of plant-derived agents known as parthenolides is also noteworthy. These agents putatively target the leukemic stem cell, which has thus far eluded prior drug development efforts. Parthenolides inhibit NF-kappa-b, which leads to activation of p53, and induce a rapid cell death in leukemic stem cells. Phase I and II studies of these agents are underway.

References

29. Knapper S, Mills KG, Kilgus AE, Austen SJ, Walsh V, Burnett AK. The effects of lestaurtinib (CEP701) and PKC412 on primary AML blasts: the induction of cytorexivity varies with dependence on FLT3 signaling in both FLT3-mutated and wild-type cases. Blood. 2006;108:3494-3503.
New Agents for the Treatment of AML: Recent Study Findings

Steven D. Gore, MD

Although there are not a large number of highly effective new drugs, a few noteworthy new treatments are emerging (Table 2). Studies reported at the 2008 American Society of Clinical Oncology (ASCO) annual meeting and elsewhere point to important new therapeutic options on the horizon.

**Clofarabine**

Clofarabine, a drug that is FDA-approved for the treatment of acute pediatric leukemia, has recently been evaluated for the treatment of adult leukemia. In a phase II study presented at the 2008 ASCO annual meeting, elderly patients with previously untreated AML experienced an overall response rate (ORR) of approximately 43%, which includes a 40% CR rate. Five percent of patients experienced CR with incomplete platelet recovery. A response rate of 56% was observed in patients between the ages of 60 and 70 years, and the response rate was 40% among patients with unfavorable cytogenetics. These are encouraging findings for a single agent in a high-risk group of patients. It must also be noted, however, that the induction mortality rate in this study was 10%.

This agent has also been studied in several combination therapy studies. In a dose-finding phase I study, patients over age 60 with de novo AML were treated with clofarabine plus cytarabine. As it turned out, the maximum tolerated clofarabine dose in this combination was lower than the initial dose level, which was excessively toxic. With the safe dose of clofarabine, 1 of 5 patients experienced a complete response to the combination. The Eastern Cooperative Oncology Group (ECOG) will conduct a follow-up study on this combination.

In a study of clofarabine with or without cytarabine, the CR rate among patients on the combination arm was 63%, a very promising outcome among the older population of patients included in the study. However, the induction mortality rate was 30%, a rate that may be considered too high to warrant use of this combination.

**Cloretazine**

Another new cytotoxic drug that has been studied recently for AML is cloretazine, an alkylating agent that is somewhat similar to cyclophosphamide. In a study of elderly AML patients, clofarabine was associated with a 35% ORR, with a CR rate of 26%. Among patients with unfavorable cytogenetics, the ORR was 23%. The induction mortality rate was 14%.

Based on these findings, a phase III randomized study evaluated cytarabine with or without cloretazine in AML patients in first relapse. The CR rate was 23% among patients receiving the combination, versus 16% among patients receiving cytarabine alone. This difference was

<table>
<thead>
<tr>
<th>Agent</th>
<th>AML Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clofarabine</td>
<td>Currently being evaluated for all AML patients</td>
</tr>
<tr>
<td>Cloretazine</td>
<td>Currently being evaluated for all AML patients</td>
</tr>
<tr>
<td>Lestaurtinib</td>
<td>FLT3-mutated</td>
</tr>
<tr>
<td>Midostaurin</td>
<td>FLT3-mutated</td>
</tr>
<tr>
<td>Tipifarnib</td>
<td>High ARS-RP1:APTX ratio (low ratio does not predict lack of response)</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Currently being evaluated for all AML patients</td>
</tr>
<tr>
<td>Decitabine</td>
<td>Currently being evaluated for all AML patients</td>
</tr>
<tr>
<td>Azacitidine</td>
<td>Currently being evaluated for all AML patients</td>
</tr>
</tbody>
</table>

Table 2. New Agents Under Evaluation for the Treatment of Acute Myeloid Leukemia
not statistically significant. However, the ORR (CR plus CR with incomplete platelet recovery [CRp]), was statistically significant with 37% versus 19% achieving remission ($P=0.004$). Unfortunately, the mortality rate was 40% and 9%, respectively, and it is thus difficult to envision this combination as a realistic therapeutic option for relapsed AML, despite the increased CR rate.

**FLT3 Inhibitors (Lestaurrentib and Midostaurin)**

Lestaurrentib and midostaurin are FLT3-targeted tyrosine kinase inhibitors currently being studied in phase II and III clinical trials for AML. In a phase II study of single-agent lestaurentib (ie, CEP701) among previously untreated older AML patients who were not candidates for intensive chemotherapy, clinical activity—defined as transient reductions in bone marrow and peripheral blood blasts or longer periods of transfusion independence—was observed among 3 of 5 patients with mutated FLT3 and 4 of 22 evaluable patients whose leukemia possessed wild-type FLT3.$^6$ These findings provided the rationale for the currently ongoing phase II and III studies, which will be discussed in the next section.

In a recent study of midostaurin (PKC412), biological activity was observed in both FLT3-mutated and FLT3-wild type AML patients.$^7$ Among 55 patients with mutated FLT3, 39 patients experienced a minimum of 50% decrement in peripheral blood blast percentage. Among 60 patients with wild-type FLT3, 23 patients experienced a similar decrement in peripheral blood blast percentage. Further studies of this agent are underway. Patients with FLT3-mutated AML comprise a high-risk subgroup, and additional data on these agents are eagerly awaited.

**Tipifarnib**

Several recent studies provide mixed indications about the potential tipifarnib for AML patients. At the 2007 ASCO meeting, Delmonte and colleagues reported a 64% CR rate among 95 patients treated with high-dose cytarabine, idarubicin, and tipifarnib as both induction and consolidation therapies, followed by maintenance therapy with tipifarnib alone.$^8$ This outcome was not necessarily better than that seen with cytarabine plus idarubicin alone; however, among patients with abnormalities in chromosomes 5 and 7—a very high-risk subset—the CR rate was 70%, which is extremely high for this population of AML patients.

Yet, Harousseau and colleagues recently reported that in a study of 457 patients over age 70 (of which 24% were over 80 years old) treated with tipifarnib versus supportive care, the median survival was 107 versus 109 days, respectively.$^9$ In addition, Erba and colleagues reported data from an intergroup study of approximately 350 AML patients over age 70 treated with 4 different schedules of tipifarnib.$^{10}$

The response rate did not exceed 20% in any of the 4 arms. Raponi and colleagues conducted a gene expression analysis to search for factors that might predict response to tipifarnib among elderly AML patients.$^{11}$ According to their report, the level of the ratio of ARS-RP1 gene to APTX gene is predictive for tipifarnib response; patients who reach a high enough ratio level have a 92% chance of responding to tipifarnib-based combination therapy. However, it is important to note that the negative predictive value—the likelihood of patients with a lower ARS-RP1:APTX ratio not responding to this treatment approach—was only 28%. In other words, a high ratio predicts response, but a low ratio does not conclusively mean that no response is likely.

**Lenalidomide**

Lenalidomide has also been evaluated in the AML setting. In one recent study, a group of elderly AML patients who received a high dose of this agent experienced decreased blast counts.$^{12}$ Although no true CRs were observed, the results indicate that lenalidomide may warrant study as part of a combination regimen.

**DNA Methyltransferase Inhibitors**

There is also interest in exploring whether DNA methyltransferase inhibitors could be useful in the treatment of AML. A randomized study of decitabine versus chemotherapy as consolidation therapy for intermediate- and high-risk AML patients in first complete remission found that decitabine was safe and well tolerated.$^{13}$ In a randomized phase II study of decitabine plus vorinostat, a histone deacetylase inhibitor, 5 of 27 patients responded.$^{14}$ In another related study, Grovdal and colleagues treated 37 AML patients and 23 MDS patients with a median age of 68 years with cytarabine–based induction chemotherapy, to which 50% achieved a CR.$^{15}$ Patients then received maintenance therapy with the DNA methyltransferase inhibitor azacitidine. The median duration of response was 13 months, with 30% of patients in remission for more than 20 months. The results are promising, but a randomized study is needed to confirm the findings.

**Immunologic-based Therapy**

New immunologic-based approaches to treating AML are also under investigation. Raza and colleagues recently reported the results of their phase I study of 18 AML patients treated with lintuzumab, a humanized anti-CD33 antibody, to which 4 patients achieved a CR with acceptable toxicity.$^{16}$

Vaccination strategies include that presented by Berneman and colleagues at the 2008 ASCO annual meeting.$^{17}$ As mentioned earlier, WT1 is frequently overexpressed in AML. Seven AML patients in remission were given
dendritic cells loaded with RNA coded for WT1, and all patients developed immune responses to WT1, with T cells that recognized WT1 circulating after vaccine administration. These data are preliminary but lead to questions about whether this strategy could be an effective way to prevent relapse of AML.

References


Future Research Directions for the Treatment of AML

Judith Karp, MD

Except in the case of APL, there are still no standards of care in the treatment of AML; currently available treatment options are not effective enough to be considered standards (Table 3). In order to further improve outcomes among these patients, new concepts and clinical trials are needed, and patients at every phase of the disease need to be enrolled in clinical trials.

During the last 10 years, investigators and clinicians have learned a great deal about the extremely heterogeneous nature of AML. New technologies are enabling us to further dissect molecular profiles and determine the prognosis associated with them. To date, the best example of this approach is the FLT3 internal tandem duplication (ITD).1,2 Investigators are now integrating available data about the nature of this AML subtype into clinical studies (Table 4).

There are at least 2 noteworthy studies focusing on AML patients with the FLT3 mutation. Based on earlier positive findings,1 lestaurtinib (CEP701) is currently being evaluated in a large study with relapsed patients in this cytogenetic subgroup. In this study, lestaurtinib is given immediately after chemotherapy.3 Also, a current clinical trial by Cancer and Leukemia Group B (CALGB) is evaluating daunorubicin with or without midostaurin, followed by consolidation and maintenance with midostaurin, a tyrosine kinase inhibitor; this trial is open only to newly diagnosed patients with AML with a FLT3-ITD. These 2 studies are prime examples of the kind of trial that our growing body of information about molecular targets makes possible.

One important caution, however, is the fact that we currently do not completely know what a drug can or will
do. Investigators often assume that a particular agent will target a particular molecule or pathway. Sometimes this assumption proves correct, but other times the agent is found to work by a completely different mechanism—an experience that has characterized the FTIs.

An ongoing phase II randomized trial is comparing 2 dose schedules of the FTI tipifarnib plus etoposide, with both drugs being given orally. A phase I study of this regimen demonstrated a CR rate of 25% among elderly AML patients with poor-risk disease.5 More specifically, the CR rate was as high as 50% for certain dose schedules; therefore, the phase II trial is evaluating the 2 schedules that elicited the highest CR rates in the phase I study. In addition, molecular profiles will be correlated with outcomes, in order to see if response can be predicted by cytogenetic subgroups.

Another area of current and future studies for AML is maintenance therapy. Maintenance therapy has been very successful in treatment of childhood acute lymphocytic leukemia and in APL, including high-risk disease.6,7 However, by using traditional chemotherapy drugs like low-dose cytarabine and other agents, maintenance therapy has not proven very effective for most subtypes of AML.

Interestingly, the study of maintenance therapy warrants the evaluating of new drugs in a single-agent fashion. For patients in whom relapse is likely, remission will probably last for less than 6 to 12 months. Because we know that no available treatment options will be curative, such patients should be given the opportunity for maintenance treatment with potentially beneficial targeted agents. For example, one recent study evaluated tipifarnib in patients with poor-prognosis AML who were in remission.8 Compared to historical controls, patients who received tipifarnib experienced a significantly longer duration of remission. This effect was seen predominantly among patients with myelodysplastic-related leukemias, treatment-related leukemias, and leukemias with abnormal cytogenetics.

Additionally, ECOG is conducting a study of tipifarnib versus placebo in the maintenance setting for patients in second or greater remission. This phase III study will test the principle initially explored in the aforementioned phase II trial of adults with poor-risk AML in first remission.8 Along these lines, an ongoing CALGB study is evaluating decitabine maintenance following standard induction therapy, followed by risk-adaptive dose intensification based on chromosomal abnormalities.

DNA methyltransferase is another exciting area of current research. One of the underlying principles behind this approach is that methylation silences genes associated with the development and/or progression of leukemia. However, whether reversing methylation could then alter the leukemogenic process remains to be determined.9,10 A CALGB study is evaluating the DNA methyltransferase inhibitor decitabine to better understand the potential role of this class of agents in the treatment of leukemia.

Another research need is the evaluation of new agents in first-line regimens. How can these new drugs be incorporated in a way that optimizes their molecular targeting abilities? Studies need to evaluate these agents in the minimal residual disease setting, the consolidation setting, and the induction setting. Single-agent maintenance therapy studies should also be considered.

Following the examples set by the FLT3 studies discussed above are other cytogenic subgroups on which we can focus. Studies have found that all-trans retinoic acid (ATRA) may have a particularly important role among

<table>
<thead>
<tr>
<th>Molecular Target</th>
<th>Agent</th>
</tr>
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<tbody>
<tr>
<td>FLT3 ITD</td>
<td>CEP-701</td>
</tr>
<tr>
<td>NPM1</td>
<td>mTor inhibitor</td>
</tr>
<tr>
<td>CEBP mutations</td>
<td>ATRA</td>
</tr>
<tr>
<td>AML-1 mutations</td>
<td>Flavopiridol (?)</td>
</tr>
<tr>
<td>Methylation (CEPBα, p15)</td>
<td>5-aza (oral?)</td>
</tr>
<tr>
<td>Translocations</td>
<td>HDAC inhibitor</td>
</tr>
<tr>
<td>VEGF</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>MCL-1 overexpression</td>
<td>Flavopiridol</td>
</tr>
</tbody>
</table>

AML=acute myeloid leukemia; ATRA=all-trans retinoic acid; FLT3-ITD=FLT3 internal tandem duplication; HDAC=histone deacetylase; mTOR=mammalian target of rapamycin; VEGF=vascular endothelial growth factor.


**Table 3.** AML: Much Work to Do

<table>
<thead>
<tr>
<th>Factor</th>
<th>&lt;55 yr</th>
<th>&gt;55 yr</th>
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<tbody>
<tr>
<td>MRD</td>
<td>33%</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>CR</td>
<td>64%</td>
<td>&lt;40%</td>
</tr>
<tr>
<td>DFS (median)</td>
<td>21 mo</td>
<td>7 mo</td>
</tr>
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<td>OS (median)</td>
<td>18 mo</td>
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AML=acute myeloid leukemia; CR=complete response; DFS=disease-free survival; MRD=minimal residual disease; OS=overall survival.
leukemias with the CEBP-alpha mutation. The cyclin-dependent kinase inhibitor flavopiridol has heightened activity in leukemias driven by vascular endothelial growth factor or that overexpress the antiapoptotic molecule MCL-1. Patients with NPM1 mutations may be explicitly sensitive to mammalian target of rapamycin (mTOR) or histone deacetylase inhibitors.

Examining these agents specifically among these patient subgroups will likely prove an effective way to increase the therapeutic armamentarium available for the treatment of AML. These targeted therapies will be most effective among patients with minimal residual disease. Therefore, intensive chemotherapy followed by a more specific targeted drug may be the optimal approach.

The ECOG is initiating a randomized phase II clinical trial to evaluate 3 promising regimens in primary refractory and relapsed AML. The first regimen is flavopiridol followed by cytarabine plus mitoxantrone, which has produced encouraging first-line results among patients with poor-risk leukemia. The second regimen combines topotecan, a topoisomerase-I inhibitor, with carboplatin—an approach pioneered by Dr. Scott Kauffman of the Mayo Clinic. The third regimen, based on work by Dr. Martin Carroll of the University of Pennsylvania, adds the mTOR inhibitor sirolimus to the MEC regimen (mitoxantrone, etoposide, cytarabine).

One of the intriguing features of this study is its incorporation of the “adaptive randomization” design. In this approach, if one regimen is found to be producing much worse outcomes than the others, that arm can be closed and the patients can be switched to another regimen.

In summary, there is much exploring to do in order to determine the optimal treatment approaches for the various subtypes of AML. The notion that molecular profiling will enable us to determine not only the prognosis but also the appropriate therapy is clearly going to be the guiding principle for both clinical trials and, increasingly, decision-making in the clinic. However, leukemia does not develop and progress on account of a single lesion—neither will treatment by attacking single lesions lead to improvement. Future therapeutic advances will most likely depend on targeting several molecules and pathways.

References

4. Levis M, Pham R, Smith BD, Small D. In vitro studies of a FLT3 inhibitor combined with chemotherapy: sequence of administration is important to achieve synergistic cytotoxic effects. Blood. 2004;104:1145-1150.
AML: Current and Emerging Treatment Approaches

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

1. AML patients with both a t(8;21) mutation and a c-KIT mutation have a prognosis that is:
   a. favorable
   b. unfavorable
   c. intermediate
   d. the prognosis associated with this combination has not been determined.

2. For AML patients with a normal karyotype, which of the following molecular markers confer a favorable prognosis?
   a. WT1
   b. FLT3
   c. NPM1
   d. EVI1

3. CEP701 and PKC412, FLT3 inhibitors currently being studied for the treatment of AML, may target which of the following?
   a. FLT3
   b. c-KIT
   c. Vascular endothelial growth factor
   d. Platelet-derived growth factor
   e. All of the above

4. In a phase III randomized study of cytarabine with or without cloretazine in AML patients in first relapse, the CR rate among patients receiving the combination regimen was:
   a. 13%
   b. 62%
   c. 23%
   d. 70%

5. In a study of cytarabine, idarubicin, and tipifarnib reported by Delmonte and colleagues, the CR rate was extremely high for patients of which cytogenetic subgroup?
   a. Mutated c-KIT
   b. t(8;21) mutations
   c. Mutated FLT3
   d. Abnormalities in chromosomes 5 and 7

6. According to a study by Raponi and colleagues, a high ratio of ARS-RP1 to APTX is predictive for tipifarnib response, and a low ratio:
   a. is predictive for no response
   b. is not predictive for no response
   c. was not observed among the patients included in the study
   d. does not appear to exist among elderly patients with AML

7. In a randomized study of decitabine plus vorinostat for AML, how many of the 27 patients responded?
   a. 5
   b. 24
   c. There were no responses.
   d. These agents have not been studied as combination therapy for AML.

8. In an ongoing clinical trial of the FLT3 inhibitor lestaurtinib, this agent is given to relapsed patients with mutated FLT3:
   a. In combination with induction chemotherapy
   b. Immediately after chemotherapy
   c. After a reduced-intensity conditioning transplantation
   d. In combination with gemtuzumab

9. ECOG is currently conducting a clinical trial of tipifarnib versus placebo for what population of AML patients?
   a. Those with mutated c-KIT
   b. Previously untreated
   c. Those in first remission
   d. Those in second or greater remission

10. According to recent reports, patients with NPM1 mutations may be explicitly sensitive to:
    a. mTOR inhibitors
    b. Histone deacetylase inhibitors
    c. Both a and b
    d. Farnesyltransferase inhibitors
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
2. Review results of clinical trials evaluating new treatment options in AML
3. Identify future research directions for the treatment of AML

**Overall Effectiveness of the Activity**

The content presented:

1. Was timely and will influence how I practice
2. Enhanced my current knowledge base
3. Addressed my most pressing questions
4. Provided new ideas or information I expect to use
5. Addressed competencies identified by my specialty
6. Avoided commercial bias or influence

**Impact of the Activity**

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.

Additional comments about this activity.

**Follow-up**

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

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**Post-test Answer Key**

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