Leading investigators discuss the management of AML in older patients, the use of cytogenetic and molecular testing in treatment planning, and emerging novel therapies.

Expert Insights Into the Contemporary Management of Older Adults With Acute Myeloid Leukemia

Farhad Ravandi, MD, Harry P. Erba, MD, PhD, and Daniel A. Pollyea, MD, MS

Introduction

Acute myeloid leukemia (AML) is a clonal, malignant disease of hematopoietic tissues characterized by the accumulation of abnormal blast cells, principally in bone marrow, and impaired production of normal blood cells. In 2013, an estimated 14,590 new cases will be diagnosed and 10,370 people will die of the disease. AML is typically a disease of older adults, with a median age at diagnosis of 67 years. Patients 60 years of age and older fare significantly worse than their younger counterparts, with 5-year survival rates of 3% to 8% in older patients compared with rates of up to 50% in younger patients. This poor survival reflects the higher frequency of adverse prognostic factors and comorbidities in older patients, as well as a preference among some physicians not to treat older patients as aggressively because of the expectation that they are less likely to benefit from intensive therapies.

The following report presents highlights from a roundtable discussion among three leading AML investigators: Farhad Ravandi, MD, from the University of Texas MD Anderson Cancer Center, Harry P. Erba, MD, PhD, from the University of Alabama at Birmingham, and Daniel A. Pollyea, MD, MS, from the University of Colorado. These experts share insights into how they manage AML in older adults and provide answers to frequently asked questions regarding the use of cytogenetic and molecular testing in treatment planning, emerging novel therapies with the potential to improve patient outcomes, and the referral of patients to tertiary cancer centers. In addition, case studies are used to illustrate selected therapeutic strategies for induction, postinduction, and postremission therapy.

What are the clinical outcomes of older vs younger patients with AML?

Dr Ravandi: AML is a disease of the elderly, and a great proportion of patients are older than 60 years of age. The traditional intensive cytarabine- and anthracycline-based regimen “3 + 7” (eg, daunorubicin 45 to 60 mg/m² per day intravenously for 3 days and...
cytarabine 100 mg/m² by continuous infusion for 7 days) has been very effective in producing remissions in younger patients, typically those younger than age 60, and about half of the patients 60 years of age and older (Table 1).

Dr Pollyea: Nevertheless, the outcomes of elderly patients with AML are suboptimal compared with their younger counterparts (Fig 1). In addition, the lack of significant improvement despite 30 years of research is quite humbling.4,5 However, I think we are now on the threshold of significant change: we will soon be able to better prognosticate those patients who would tolerate and respond to some of our more conventional therapies, we are learning more about the biology of this disease, and we have multiple promising novel therapies on the horizon that will expand the pool of patients who will have clinically significant responses and better outcomes than we have seen historically.

Dr Erba: What we’ve learned over the past several decades about the treatment of older patients with AML is that in general they do not tolerate chemotherapy as well as younger patients do, remission rates are lower, and event-free and overall survival are inferior. However, we do need to keep in mind that cytarabine and anthracycline still form the backbone of treatment. Some older patients will achieve long-lasting remissions and can potentially be cured of their disease with traditional intensive chemotherapy. What’s important for the practicing clinician is to identify those patients who may benefit from intensive chemotherapy and not to avoid it solely on the basis of age. Conversely, for patients with an antecedent hematologic disorder or complex karyotypes who we know do less well with chemotherapy, I think it is reasonable to consider alternative options, preferably in clinical trials. A number of agents in the pipeline now are less intensive than standard chemotherapy, which we’ll discuss later.

Dr Ravandi: It is important to remind treating practitioners not to be nihilistic about older patients. An analysis of the SEER registry by Meyers et al6 revealed that more than half of elderly patients did not receive any chemotherapy. However, a lot of data are now available to suggest that any form of therapy, even simple treatments such as low-dose cytarabine (Ara-C), may be beneficial to older patients. For example, Juliusson et al2 looked at six different regions in Sweden that varied with regard to treating AML in the elderly. In those regions where intensive induction therapy was more common, better outcomes were observed. A subset of older adults — those with intact functional status, minimal comorbidity, and favorable cytogenetic/molecular mutations — can thus benefit from intensive chemotherapy.

### Table 1. — Common Induction Regimens Used in the Treatment of Older Patients With AML

<table>
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<tr>
<th>Regimen</th>
<th>Outcomes of Selected Studies</th>
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<tr>
<td>Standard “3 + 7” induction with cytarabine (100-200 mg/m² infusion × 7d) and anthracycline (daunorubicin, idarubicin, or mitoxantrone × 3d)</td>
<td>3 + 7 vs supportive care: OS was longer and CR rate was higher (58% vs 0%); hospitalization rate similar.4 Swedish study: Standard intensive treatment in older pts improves early death rates and long-term survival compared with palliation.2</td>
<td>A subset of older adults — those with intact functional status, minimal comorbidity, and favorable cytogenetic/molecular mutations — can thus benefit from intensive chemotherapy.</td>
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<tr>
<td>3 + 7 regimen with intensified-dose daunorubicin (90 mg/m² daily)</td>
<td>The higher dose was associated with increased CR, 2-yr EFS, and 2-yr OS in pts aged 60 to 65 yrs.42</td>
<td>There were no significant differences between the two groups in the incidence of hematologic toxic effects, 30-day mortality, or the incidence of adverse events.</td>
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<tr>
<td>LDAC (20 mg twice daily for 10 days, at 4- to 6-wk intervals)</td>
<td>LDAC vs best supportive care/hydroxyurea: 18% of older pts given LDAC achieved CR vs 1% receiving supportive care.41</td>
<td>The survival advantage was not seen in pts with adverse cytogenetics. Toxicity scores and supportive care requirements did not differ between the treatment arms. Induction death occurred in 26% of pts.</td>
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<tr>
<td>Azacitidine (75 mg/m² per day)</td>
<td>Azacitidine vs conventional care regimens: CR rate was similar but median survival (24.5 vs 16 mos) and 2-yr OS (50% vs 16%) were significantly better.40</td>
<td>Azacitidine was better tolerated than conventional regimens, with fewer infections and fewer incidences of hospitalization.</td>
</tr>
<tr>
<td>Decitabine (20 mg/m² daily for 5 days, repeated monthly)</td>
<td>Decitabine monotherapy: CR was 24%, with a median EFS and OS of 6 and 8 mos, respectively.46 Decitabine vs LDAC or BSC: Decitabine increased CR rate (18% vs 8%) but had little effect on OS.49</td>
<td>The 30-day mortality rate was 7%, and the most common toxicities were myelosuppression, febrile neutropenia, thrombocytopenia, anemia, and fatigue.</td>
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CR = complete remission, EFS = event-free survival, pts = patients, ORR = overall response rate, LDAC = low-dose Ara-C, OS = overall survival, BSC = best supportive care
reported: higher responses and longer survival. Of course, not everyone in those regions was cured, but I think it’s important to highlight that even the older population can often tolerate intensive therapy. As Dr Erba mentioned, in some of these patients, traditional Ara-C and anthracycline can be very effective.

Dr Pollyea: I think that the power of the Swedish study is that it takes some element of selection bias out of the equation, which is one of the problems when you review the literature trying to decide what’s best for your patients. I think selection bias plays a huge role in some clinical trials, so population-based studies, such as the Swedish one, are really useful to get a different perspective. I think we all agree that age is a very important factor in making some of these decisions, but like Dr Erba said, I think it is clear that age is not the most powerful predictor of outcomes.

**Dr Erba:** Cytogenetic and molecular data can help us identify patients who can benefit from standard chemotherapy and those who won’t benefit and who should be considered for alternative approaches (Table 2). I agree with Dr Ravandi in that some treatment is likely better than no treatment. However, there are only two randomized clinical trials that address this issue. Twenty years ago, French researchers looked at low-dose Ara-C vs an anthracycline- and cytarabine-based regimen and found a higher remission rate with anthracycline and cytarabine but more toxicity and no difference in overall survival. Another study, from Löwenberg et al., showed that when the 3 + 7 regimen (or a 3 + 7-like approach) was compared to palliative treatment with hydroxyurea, there was a survival benefit. No studies in the modern era have looked at low-intensity regimens compared with more intensive therapy. However, a retrospective analysis showed that the survival of older patients is not impaired if you begin treating them with a less intensive therapy such as hypomethylating agents compared with an intensive cytarabine-based regimen.

The reason why I think cytogenetic and molecular data are important is that there is some information — for example, core-binding factor (CBF) translocations, mutant nucleophosmin (NPM1) without Fms-like tyrosine kinase 3 (FLT3)-activating mutations, or mutations in CCAAT/enhancer binding protein-alpha (CEBPA) — that potentially confers higher response.

**How can prognostic factors guide therapy in older patients with AML?**

**Dr Pollyea:** We all appreciate how powerful cytogenetics can be for prognosis, but how does that influence your upfront treatment of elderly patients with AML when you may not have the data at the time of diagnosis? Do you wait or do you typically treat before having the results of cytogenetic testing?
rates and superior event-free and overall survival compared with older patients who do not have those characteristics, when treated with standard induction chemotherapy (Fig 2). So I primarily use cytogenetic and molecular data to select patients that I want to approach in a curative fashion. Conversely, if the cytogenetic or molecular data suggest that the patient will not be cured by the standard anthracycline/cytarabine approach, then I would consider alternative, less intensive therapies that are commercially available, such as hypomethylating agents, or an appropriate clinical trial.

My final point on this issue is that if the patient is 60 years old and has high-risk cytogenetics or poor-risk molecular markers, I'm not certain that it matters how you get that patient into a remission. However, if you get a remission and you still want to consider a curative option in that genetic subset, all roads lead to an allogeneic transplant with a reduced-intensity conditioning regimen. For an older patient with poor-risk cytogenetics or a history of antecedent hematologic disorders, I think it’s appropriate to consider less intensive therapies. However, if the patient responds and his or her performance status and organ function are good, don’t forget that you can still consider potentially curative options for those older adults.

Dr Ravandi: It is important to obtain cytogenetic and molecular data whenever possible. Sekeres et al10 looked at patients from MD Anderson and the Cleveland Clinic with a white blood cell count of < 50,000/mm³ and found that there was no worsening of outcome if you waited 5 days to get the molecular and genetic data in the elderly population compared to if you went ahead and treated straight away. I don’t think physicians would lose anything in older AML patients without proliferative disease to wait a few days to get the cytogenetic and molecular data and use them exactly as Dr Erba suggested.
**Dr Pollyea:** I think that’s an important point: practitioners who see patients with AML in the community should appreciate that cytogenetic and molecular information can guide treatment decisions in the first-line setting. It’s no longer an “over-the-shoulder” look to decide whether or not a patient should get consolidated with a transplant. It actually does have implications for upfront treatment strategies, not only in the experimental realm for purposes of clinical trials, but also for making real treatment decisions in the clinic. I agree with Dr Erba that for a patient over age 60, the key to long-term survival or cure is getting that patient through an allogeneic stem-cell transplant. Those with antecedent hematologic disease or complex karyotype have less of an ability to respond to intensive regimens, so these are the issues that need to be considered upfront in order to select the optimal therapy for the patient.

**Which emerging molecular and cytogenetic prognostic factors are most relevant to the community practitioner?**

**Dr Ravandi:** At the moment, I think the only factors that are clinically significant are FLT3, NPM1, and CEBPA. Those factors have enough data to suggest that they can affect, at minimum, postremission therapy. There are other molecular aberrations that are going to be important — for example, IDH1, IDH2, and MLL — but the literature is not yet sufficient to recommend those be tested by the community physician. There are also some data that suggest that the presence of mutated c-KIT in patients with core-binding factor leukemias is associated with an adverse outcome, but whether these data should lead to a change in therapy will need to be answered by ongoing clinical trials.

**Dr Pollyea:** There are going to be some practice-changing findings coming out in the new molecular era. Already, in younger patients, DNA methyltransferase 3A (DNMT3A) status, as well as NPM1 and MLL, impacts upfront induction chemotherapy treatment choices. Also, inhibiting IDH in patients with an IDH mutation is certainly on the horizon. Although it’s premature to make a recommendation that DNMT3A, IDH, and MLL testing needs to be part of everyone's standard clinical practice pattern, I do feel strongly that it would be in our patients’ best interests to have these and other genes tested, if not for making frontline treatment decisions, then for treatment of relapses when they occur. I think we’re right on the cusp of these tests becoming standard.

**Dr Erba:** For the practicing hematologist/oncologist in the community, I think there are some important points to be made in terms of routine clinical practice. When you see older patients with cytopenias and you’re performing a marrow, it’s important to do the cytogenetic analysis as well as test for the molecular markers NPM1, FLT3, and CEBPA. Physicians need to understand that cytogenetics can be done on peripheral blood even with few circulating blasts because those will be the ones that divide in culture. So it is at least worth an attempt to get those studies done on peripheral blood when you have a dry tap. At the end of the day, this testing is important enough that you should go back and repeat a marrow if you have to, in order to collect that information. It does help in prognostication and in choosing the most appropriate therapies for these patients.

**Dr Ravandi:** Cytogenetics is obviously imperative, but it is a work in progress. As whole genome and exome sequencing becomes cheaper and cheaper, we may in the near future see a further subclassification of AML based on various pathways discerned with sequencing. At the moment, I think cytogenetic testing is critical and molecular testing for FLT3, NPM1, and CEBPA is useful. Further, there are novel agents that may be approved in the next several years that could actually directly affect these aberrant molecular pathways.

**Are there any prognostic scoring systems that the practicing oncologist can use to decide which patients are suitable for intensive therapy and which patients are not?**

**Dr Pollyea:** I believe there are some really good scoring systems, particularly the MD Anderson system and the online AML-SCORE. Although I think that some of the data for the AML-SCORE calculator are not typically thought of as prognostic for AML, such as temperature and fibrinogen, I’ve used it as a tool when subjective analysis is insufficient. We can rely on experience for a lot of decisions, but since this disease is infrequently encountered in the community, it helps to have some validated data points. I would also like to see these prognostic scores incorporated more in the reporting of clinical trials.

**Dr Erba:** I agree that we need to examine prognostic factors prospectively. It’s not quite clear if the negative impact of traditional prognostic factors such as performance status is as important today as it was in the past. As an example, we know that SWOG investigators have looked at five clinical trials that were done — two in patients younger than age 55 and three in patients older than age 55 — and they found a very clear correlation between early mortality, age, and performance status. Patients with a
performance status of 2 or 3 who were over the age of 65 had over 30% induction mortality with the 3 + 7 regimen. However, we’ve recently looked at our data from the 1990s, and it’s not clear that induction mortality is as dismal as it seems from those older studies with older patients. The one caveat is that over the last decade, as other less intensive therapies and experimental protocols have become available, physicians have been reluctant to treat older patients with 3 + 7. I think we’re in some ways selecting against the older, more infirm patients on these clinical trials. In order to do this research correctly, we have to incorporate modern scoring systems and geriatric assessment tools that include scores of fitness for chemotherapy, performance of activities of daily living, and so on.

Dr Ravandi: Yes, I agree. For example, at MD Anderson, we use the score published by Kantarjian et al to select therapy for patients over the age of 60 up to about 70 years. One point of that score is a creatinine level of > 1.3 mg/dL, which can be used to select against a fair number of patients over the age of 60 so that they are not treated with Ara-C/anthracycline-based therapy. The UK Medical Research Council (MRC) also has a similar scoring system, which they report in all of their trials. As Dr Pollyea mentioned, the German AML-SCORE tool is useful as well. All these systems, however, are continually evolving and so will likely need to be refined as new supportive care strategies and new treatment regimens become standard.

Table 3. — Selected Novel Agents Under Investigation in Older Patients With AML

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Phase</th>
<th>Outcomes of Selected Studies</th>
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<tbody>
<tr>
<td>Gemtuzumab ozogamicin</td>
<td>Anti-CD33 antibody conjugate II</td>
<td>III</td>
<td>First-line gemtuzumab vs standard chemotherapy in pts aged 50–70 yrs: CR/CRp was 81% vs 75%, 2-year EFS was 41% vs 17%, and OS was 53% vs 42%; benefit was seen mostly in patients with favorable- and intermediate-risk cytogenetics.</td>
</tr>
<tr>
<td>Clofarabine</td>
<td>Purine nucleoside analogue II, III</td>
<td>II, III</td>
<td>First-line monotherapy in older pts with unfavorable prognostic factors: ORR was 46% (38% CR, 8% CRp); DFS was 37 wks, OS was 41 wks. Clofarabine + cytarabine vs placebo + cytarabine in R/R older pts: ORR was 47% (35% CR) vs 23% (18% CR); OS, DFS, and DOR were similar in both arms.</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Immunosomodulatory agent I/II</td>
<td>I/II</td>
<td>First-line azacitidine then lenalidomide in older pts: ORR was 40%, including 28% CR/CRi; AEs were gastrointestinal, fatigue, and myelosuppression.</td>
</tr>
<tr>
<td>CPX-351</td>
<td>Liposomal daunorubicin and cytarabine</td>
<td>IIb</td>
<td>First-line CPX-351 vs 3 + 7 regimen in older pts: CR/CRi was 69% vs 27%, median EFS was 9 mos vs 1 mo, median OS was 11 vs 6 mos, and 60-day mortality was 4% vs 40%.</td>
</tr>
<tr>
<td>Quizartinib</td>
<td>FLT3 kinase inhibitor II</td>
<td>II</td>
<td>Monotherapy in R/R older pts: for FLT3-ITD–positive pts, the composite CR rate was 54%, median DOR was 12.7 weeks, and median OS was 25.3 wks, significantly higher than for FLT3-ITD–negative pts.</td>
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<tr>
<td>Volasertib</td>
<td>Polo-like kinase (PLK1) inhibitor</td>
<td>II</td>
<td>First-line volasertib + LDAC vs LDAC in elderly pts: CR/CRi was 31.0% vs 11.1%; a trend for EFS benefit was also observed; remissions were observed across all genetic groups; common AEs were febrile neutropenia, constipation, nausea, and anemia.</td>
</tr>
<tr>
<td>Tosedostat</td>
<td>Aminopeptidase inhibitor II</td>
<td>II</td>
<td>Monotherapy in R/R pts: 10% CR/CRi; most common AEs were febrile neutropenia and thrombocytopenia.</td>
</tr>
<tr>
<td>Vosaroxin</td>
<td>Topoisomerase II inhibitor II, II</td>
<td>II</td>
<td>Monotherapy in R/R pts: 7% CR/CRi; major dose-limiting toxicity was stomatitis. Vosaroxin + cytarabine in R/R pts: ORR was 29%, including 25% CR; median OS 7.1 mos.</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Proteasome inhibitor I, II</td>
<td>I, II</td>
<td>First-line bortezomib + decitabine: 37% CR/CRi. First-line bortezomib + daunorubicin/Ara-C: 69% CR/CRi.</td>
</tr>
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R/R = relapsed/refractory, CR = complete remission, CRi = CR with incomplete blood count recovery, CRp = CR with incomplete platelet recovery, pts = patients, ORR = overall response rate, AE = adverse event, LDAC = low-dose cytarabine, DOR = duration of response, DFS = disease-free survival
in older patients with AML; it was first approved in May 2000 as a single agent for older patients with relapsed AML who were considered to be not suitable for chemotherapy. Approval was based on phase II studies that showed a 25% to 30% complete remission (CR) plus CR with incomplete platelet count recovery (CRi). After it came into routine clinical practice, many of us saw that the drug was given to older, frail individuals who had very refractory leukemias. Unfortunately in that situation, we saw more of the toxicity than the benefit of the drug, and the initial enthusiasm waned. Then came the SWOG study that combined gemtuzumab single dose on day 4 with standard anthracycline and cytarabine that showed no improvement in CR rates, disease-free or overall survival, and unfortunately a higher induction mortality. So the FDA asked the manufacturer to remove the drug from the market, which it did voluntarily.

However, that decision may have been premature because very shortly after that a number of studies were published involving older patients and combining gemtuzumab with chemotherapy. The most exciting of these was the French Acute Leukemia French Association ALFA-0701 study in which gemtuzumab was given at a total dose of 9 mg/m² but in a novel fractionated schedule of 3 mg/m² on days 1, 3, and 5, with a standard daunorubicin and cytarabine including daunorubicin 60 mg/m². While no difference was seen in CR rates between the gemtuzumab-containing arm and standard chemotherapy, a significant improvement in event-free and overall survival was reported in patients between the ages of 50 and 70 years. The benefit was seen mostly in patients with favorable- and intermediate-risk cytogenetics, not in the poor-risk cytogenetic group. In addition, there was a benefit even in the older patients in that age group, those between 65 and 70 years. There were three cases of hepatic veno-occlusive disease (VOD), one of which was fatal and associated with the gemtuzumab. Nonetheless, many of us believe that the withdrawal of gemtuzumab was premature and that it is actually an active agent, especially in older patients.

I have been closely involved in the development of the purine nucleoside analogue clofarabine as a single agent for the treatment of older patients with AML. Dr Kantarjian and I led a phase II study in the United States of older AML patients with high-risk features. The overall response rate was 45%. What was really intriguing to us is that when we looked at patients with high-risk cytogenetics or antecedent hematologic disorders, the response rates were similar to those who did not have those high-risk features. In terms of toxicity, the induction mortality was just under 10%, with about a 20% to 25% rate of reversible hepatic toxicity and about a 5% rate of renal toxicity, again mostly reversible. It’s now being tested in an ECOG trial looking at clofarabine vs standard daunorubicin and cytarabine for older patients.

**Dr Pollyea:** I think lenalidomide is another interesting agent for the treatment of AML. It’s an active agent, and we’ve been working for several years to determine what setting is ideal, at what dose, and with what other agents. We did a phase I study followed by a phase II study of sequential therapy with azacitidine followed by a high dose of lenalidomide and had some promising results. We saw a 40% overall response rate and close to a 30% CR rate so there is a significant minority of patients who do respond to this regimen, and that was in the elderly population. Although the mechanism is not well understood, it does appear that lenalidomide is an active drug for elderly AML patients. We’re now piloting this regimen in relapsed and refractory patients to see what the activity is in that setting. There is also a company-sponsored trial comparing the sequential combination with high doses of lenalidomide followed by more maintenance doses, which has been piloted by Washington University. We’re doing that in a controlled randomized fashion to determine which of these two regimens may be more effective for this population.

**Dr Erba:** A hypomethylating agent that has been approved for myelodysplastic syndrome (MDS) and is used for AML is decitabine. The Ohio State University group published some interesting data regarding a 10-day course of decitabine using what we refer to as the “MD Anderson dosing schedule” of 20 mg/m² intravenously over 1 hour on days 1 to 10 of 4-week cycles. The researchers saw encouraging response rates: 42% of patients achieved CR and 58% achieved either CR or CRi. In addition, a phase III trial comparing decitabine to either supportive care or low-dose Ara-C showed a statistically nonsignificant but favorable trend for increased overall survival for patients treated with decitabine, from 5.0 to 7.7 months. Unfortunately, because of the statistical design of the study, the drug did not receive approval for use in older AML patients. The other hypomethylating agent used off-label in this setting is azacitidine. Several recent studies have shown that azacitidine either prolongs overall survival compared to conventional regimens or has similar efficacy but a better toxicity profile in older patients with AML.

**What are some promising agents with novel MOAs currently in clinical development?**

**Dr Ravandi:** One new class of agents is the FLT3 kinase inhibitors, the most potent and specific of which is quizartinib (AC220). It has been evaluated in a phase II study as a single oral agent in the relapse...
setting in older FLT3-ITD–positive patients who were in first relapse or primary refractory disease.\textsuperscript{31} The overall composite CR rate (CR + CRi) was 44\% to 47\%. Essentially, the drug was able to clear the marrow from leukemic cells in the first relapse setting in almost half of heavily pretreated patients. That is quite remarkable because we have been using combination chemotherapy regimens in the relapse setting in AML for many years, and if a regimen produces a 35\% response rate, we consider it active, even in the younger patients. We also recently reported the results of a study combining another FLT3 inhibitor, sorafenib, plus 5-azacytidine in patients with FLT3-ITD–positive AML, and we saw approximately a 50\% response in very heavily pretreated patients.\textsuperscript{32} So I think these FLT3 kinase inhibitors are potentially active agents, and I would encourage practicing oncologists to refer their patients to these trials.

**Dr Ravandi:** Three other novel agents are worth mentioning (Table 3). The first is CPX-351, a liposomal formulation of cytarabine and daunorubicin in a 5:1 molar ratio, which is being evaluated in untreated older AML patients and secondary AML.\textsuperscript{33} The phase IIb study presented at ASH 2012 compared up to 2 induction and 2 consolidation courses of CPX-351 with standard 3 + 7 therapy. Patients treated with CPX-351 showed marked improvements in CR + CRi rate, median event-free survival, and overall survival. This activity was seen in all subgroups, including patients with adverse cytogenetics. Second, a first-in-class quinolone derivative topoisomerase II inhibitor called vosaroxin potentially offers advantages over anthracyclines, including less risk of off-target organ damage (eg, cardiotoxicity). It was shown in a phase II trial\textsuperscript{34} to have an overall response rate of 28\%, most of which were CRs, with an acceptable safety profile. It is currently being evaluated in combination with cytarabine in a large randomized phase III trial in patients with relapsed AML. If vosaroxin becomes available, it will be an important drug to consider in the elderly, perhaps in combination with Ara-C or hypomethylating agents. Third, a particularly interesting new drug is volasertib, which is a polo-like kinase (PLK1) inhibitor that was reported by Dohner et al\textsuperscript{35} at ASH in 2012. PLK1 is essential for cell division, specifically for spindle assembly during mitosis. Volasertib was evaluated in a randomized phase II trial of newly diagnosed older patients ineligible for intensive therapy who received low-dose Ara-C plus or minus volasertib. The volasertib arm was associated with an almost 3 times higher response rate and better event-free and overall survival. A phase III trial of volasertib called POLO-AML-2 was initiated in early 2013, so that’s another agent that’s potentially going to find its way to the treatment of older AML patients.

**Dr Erba:** What was most impressive about the volasertib data that Dr Dohner presented was the high response rate, even in patients with complex karyotypes.

**When is referral of older patients with AML to a tertiary center warranted?**

**Dr Ravandi:** I believe that as many AML patients as possible should be treated at academic institutions, not because we are any better than community oncologists but because we have access to a number of resources not generally available, including pretreatment testing and banking and multiple clinical trials. In general, I would recommend that all practitioners consider sending their patients with acute leukemia to academic centers.

**Dr Erba:** I agree. I would also say that AML is a rare malignancy that the community oncologist is going to see fewer than 5 to 10 times per year. Even with less intensive therapies, it will require hospitalization of the patients due to the complication of bone marrow failure. What the academic-centered setting offers is continuous monitoring of these patients by house staff as well as a variety of consultative services. The other point is that for many patients with AML, the only potentially curative option is allogeneic transplant. So another advantage is that your patients are at a center where tissue typing and donor searches can be done early and the patient may more seamlessly go to a transplant. In the community setting, it’s difficult to get that patient into see the transplanter at the academic center and have the patient evaluated in a timely fashion while you are also trying to give very intensive chemotherapies and dealing with those complications.

**Case Study in Induction Therapy**

*A 62-year-old woman presents with low-grade fever, anemia, thrombocytopenia, and leukopenia. She has no comorbid conditions, no antecedent hematologic disorder, and normal organ function. A bone marrow examination revealed M1 AML and diploid cytogenetics.*

**Dr Erba:** The molecular diagnostics would be very important in this case. If the patient is FLT3-ITD–negative and NPM1-mutated or CEBPA-mutated, I might be even more optimistic. But even if I didn’t have those data, we have a 62-year-old woman who has no comorbidities, no complications of the disease at this point, and normal organ function, so I would consider standard therapy or a clinical trial that...*
incorporates standard therapy. Then, based on the molecular testing results, I would consider high-dose Ara-C consolidation or transplant. There aren’t a lot of data indicating that a transplant actually benefits patients who are FLT3-ITD-mutated and in remission, but that’s what we tend to do.

**Dr Pollyea:** Dr Erba, do you have an age cut-off for high-dose Ara-C consolidation?

**Dr Erba:** I go into the early 70s but only up to a total dose of 1 g/m². Some of the most impressive long-term disease-free survival data came from an older ECOG study,36 in which they used Ara-C at 2 g/m² twice daily for 6 doses.

**Dr Ravandi:** I agree that such a patient could easily benefit from Ara-C and anthracycline-based induction either on or off a clinical trial. At MD Anderson, we use a higher dose of Ara-C: 1.5 g/m² daily plus idarubicin for 3 days. For younger patients, we give it for 4 days. I think that there is some revised thinking about the whole dosing of Ara-C induction based on a study from Löwenberg et al37 and other papers, which indicated that perhaps high doses of Ara-C are not necessary and that intermediate doses may be better than standard doses.

**Dr Pollyea:** I’m not so sure how convincing the data are for consolidation in elderly patients fit for intensive induction chemotherapy. Whether patients receive consolidation with cytarabine and for how many cycles are open questions that need to be ad-

dressed in the setting of clinical trials. Consolidation with further cycles of cytarabine usually doesn’t enter the equation for me because the supportive care measures and transplant protocols have gotten so good (Table 4).

**Dr Erba:** I agree. If I have older patients in their 70s or above with high-risk cytogenetics, and they get through induction, I would tell them that they should take this time and enjoy life. I would not put them through consolidation because I am not certain of the benefit. It might benefit a small percentage of patients, but the jury is still out.

**Case Study in Post-Induction Therapy**

A 74-year-old man was diagnosed with AML (normal karyotype, NPM1-positive, FLT3-ITD-negative) and received standard-dose cytarabine/anthracycline induction therapy. Ten days following completion of induction therapy (day 14), he underwent a bone marrow biopsy that revealed residual blasts (8%) and no hypoplasia.

**Dr Erba:** This case is a great example to include in a roundtable discussion because you will not find any textbook, evidence-based information on what to do with day 14 bone marrow results. At this point, you could argue that it is possible that you are seeing the beginning of marrow recovery in this patient. I do not know that those residual blasts are the same as in the original leukemia, or maybe it is persistent

### Table 4. — Supportive Care Practices for Patients With AML*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal infections</td>
<td>Azole antifungals (posaconazole, voriconazole, echinocandins, amphotericin-B)</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>Broad-spectrum antibiotics</td>
</tr>
<tr>
<td>Viral infections</td>
<td>Acyclovir, valacyclovir</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>Hydroxyurea</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>G-CSF (filgrastim), GM-CSF (sargramostim) during postremission therapy</td>
</tr>
<tr>
<td>Anemia/thrombocytopenia</td>
<td>Use leukocyte-depleted products for transfusion and irradiated blood products for patients receiving immunosuppressive therapy; HCT candidates should be screened for CMV</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>Prophylaxis with IV hydration with diuresis, urinary alkalinization, allopurinol; treatment with rasburicase</td>
</tr>
<tr>
<td>Cognitive decline/cerebellar toxicity</td>
<td>Patients should be monitored for nystagmus, dysmetria, slurred speech, and ataxia before each dose of cytarabine</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>Serotonin receptor antagonents (ondansetron)</td>
</tr>
<tr>
<td>Ocular toxicity</td>
<td>Saline or steroid drops in both eyes during cytarabine therapy</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>Mouthwash with viscous lidocaine, Maalox, and injectable diphenhydramine liquid</td>
</tr>
</tbody>
</table>

* References 51-55.
disease. On the other hand, there is nothing magical about a marrow that every single last blast cell should be gone. Perhaps if you repeated the marrow a week later, it would look better. By saying no hypoplasia, I’m assuming that the marrow has been cyto-reduced; otherwise, if it is only 8% blasts, what are those other cells? At this point they’re probably lymphocytes. Putting it all together in this case, I would tend to watch the patient since it seems that he’s had cytoreduction but just not a marrow aplasia. I would watch him for another week and repeat a marrow if his counts were not recovering, even if I knew that those 8% blasts were the myeloid blasts.

Dr Ravandi: When using a higher dose of Ara-C, virtually everyone is going to be hypoblastic on day 14. My understanding from the CALGB studies is that on day 14, if the patient has more than 20% cellularity and more than 5% blasts, he would be given a second abbreviated course of 2 + 5. No hypoplasia probably means that the cellularity is more than 20% and, of that, 8% of cells are blasts. Then the question becomes: would you do the same thing in the 74-year-old as you would in a 55-year-old? If the patient was age 55, I would likely give a second course because the research shows that patients who receive 2 cycles of induction using the traditional 3 + 7 regimen fare just as well if they achieve a remission as those who receive 1 cycle.38 So for a younger patient, I would probably give a second abbreviated course but probably not in this 74-year-old patient.

Dr Erba: I agree. What’s occurring at that time with this patient is clearly important. You often do not get a great aspirate on day 14 because the marrow is hypocellular, so I take this information with a large grain of salt. I try not to give more induction at this point. I would argue that you could interpret the data from Rowe et al38 in a way that suggests that we do not really know the clinical significance of a minor amount of residual disease on day 14. I think that residual disease is an area that we know very little about and have made up these algorithms to make us feel better. For example, in the current SWOG 1203 trial, we’re comparing 3 inductions for younger patients: cytarabine and daunorubicin or idarubicin and cytarabine with or without vorinostat. To make the 3 arms equivalent, we put in a day 14 bone marrow, but there are no guidelines on what to do with that information. It has raised a lot of questions among investigators.

Dr Pollyea: This example is where your experience is really helpful, Drs Erba and Ravandi. What concerned me when looking at this case was not so much the residual blasts but the lack of hypoplasia in a patient who was treated with an intensive regimen. I would probably recommend more chemotherapy. However, proceeding cautiously is certainly important, since it’s always possible to see latent responders, particularly with patients treated with clofarabine. There are times when patience is the best prescription, and appreciating this approach is truly an art that only comes with experience.

Dr Erba: From my own practice, I have a patient on the clofarabine arm of the ECOG 2906 study who at day 14 had a 10% cellular marrow and 10% blasts. I decided to wait, and he achieved CR without any further treatment. When the fellow rushed back to me and said that there was residual disease in that marrow — 10% to 20% cellular and 8% blasts — my next question was, “What are the other 92% of the cells?” If they are developing erythroid and granulocytic precursors, it might be early marrow recovery, so the context is very important.

Case Study in Postremission Therapy

A 71-year-old man with a history of AML presented with inv(16). He was treated with 3 + 7 induction therapy and achieved CR. A post-induction biopsy revealed no residual blasts (<5%) and no hypoplasia.

Dr Ravandi: I would continue to treat this patient with Ara-C consolidation. This case involves an older patient with core-binding factor (CBF) leukemia. The data from Applebaum et al14 showed that older patients with CBF leukemias tend to do worse than younger patients perhaps because their residual stem cell reserve is less healthy. In general, CBF leukemia patients should be treated with Ara-C as much as possible because they are sensitive to it. The MRC study39 and the French ALFA study22 showed a benefit for patients with CBF leukemias when gemtuzumab was added to chemotherapy. However, in terms of practicing oncologists, it is a moot point because gemtuzumab is no longer available. Therefore, I would consolidate this patient with perhaps 4 courses of high-dose Ara-C, approximately 5 to 10 g/m².

Dr Erba: I would give this patient high-dose Ara-C consolidation. I usually do 6 doses at 1 g/m², right in the range of what Dr Ravandi does. As far as the number of cycles, 4 is a good goal, but 2 or 3 is also acceptable, depending on how the patient responds. The optimal number of cycles is really unclear, especially in older patients.

Dr Ravandi: They should be given as many cycles as they can tolerate — up to 4 using the CALGB regimen.
CBF leukemias are really the most ARA-C-sensitive leukemias, and when these patients relapse, they do not always fare well. You want to avoid them relapsing. For consolidation therapy in these patients, we administer up to 6 cycles of the FLAG regimen (fludarabine, Ara-C, and G-CSF).40

References


