

CE

# The Oncology Nurse's Role in AML Management: Focusing on the Patient in an Era of Novel Therapy

PeerView  
inReview

**Course Director**



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**What's Inside**

- 3 AML Diagnosis, Prognosis, and the Evolving Role of Novel Cytotoxic Agents
- 8 Targeted Therapies for Patients With AML: Current and Future Directions



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## Activity Information

### Activity Description and Educational Objectives

In this activity, an oncology nurse expert discusses new developments in the management of patients with acute myeloid leukemia (AML), including evidence on emerging therapies in various AML populations and practical considerations on their use relevant for patient care.

Upon completion of this activity, participants will be able to:

- Educate patients on the wide diversity of AML presentations, including clinical implications of high-risk disease, early versus late relapse, and secondary AML
- Answer patient questions on novel cytotoxic and targeted treatment options in the AML setting
- Cite evidence on the safety and efficacy of novel and emerging treatments in AML
- Manage treatment-emergent toxicity in patients with AML, including those receiving upfront therapy and individuals with a longer treatment history

### Target Audience

This activity has been designed to meet the educational needs of hematology-oncology nurses and other clinicians involved in the management of patients with AML.

### Nursing Education Purpose Statement

The purpose of this activity is to improve knowledge and competence of nurses concerning the treatment of acute myeloid leukemia (AML).

### Requirements for Successful Completion

In order to receive credit, participants must view the activity and complete the post-test and evaluation form. A score of 70% or higher is needed to obtain CE credit. There are no pre-requisites and there is no fee to participate in this activity or to receive CE credit. Statements of Credit are awarded upon successful completion of the post-test and evaluation form.

Media: Enduring Material

Release and Expiration Dates: December 16, 2016 - December 15, 2017

Time to Complete: 60 minutes

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Sara M. Tinsley, PhD, ARNP, AOCN, has a financial interest/relationship or affiliation in the form of:

*Consultant* for Pfizer.

*Speakers Bureau* participant with ARIAD Pharmaceuticals, Inc.; Celgene Corporation; Incyte Corporation; and Novartis Pharmaceuticals Corporation.

Sara M. Tinsley, PhD, ARNP, AOCN does intend to discuss either non-FDA-approved or investigational use for the following products/devices: CPX-351, vosaroxin, midostaurin, gilteritinib, vadastuximab, selinexor and other novel targeted or antibody-based approaches to treating AML.

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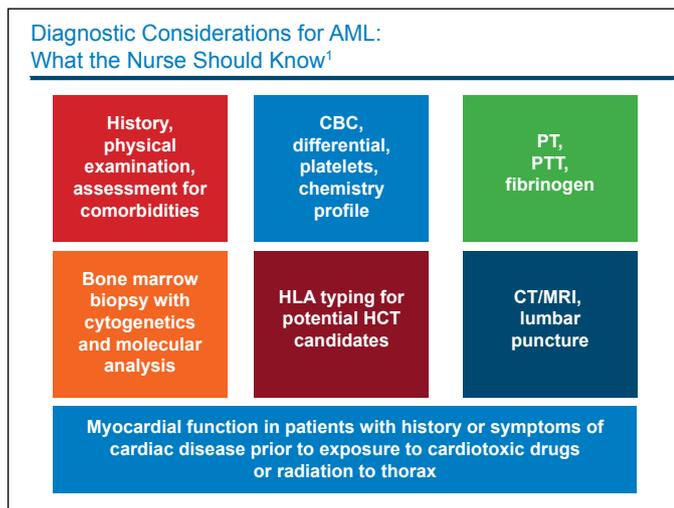
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# The Oncology Nurse's Role in AML Management: Focusing on the Patient in an Era of Novel Therapy

## AML Diagnosis, Prognosis, and the Evolving Role of Novel Cytotoxic Agents

**Dr. Tinsley:** Hello. This is Dr. Sara Tinsley from the Moffitt Cancer Center in Tampa, Florida. Welcome to this educational activity on the nurse's role in managing acute myeloid leukemia. This is an exciting time in AML, as several novel agent classes may soon be available for use in the clinic, pending FDA approval. We'll explore the evidence behind these strategies today and discuss how nurse professionals can be prepared for their use.

After completing this activity, access the post-test and evaluation form by clicking the red Get Certificate button. I encourage you to download the slides, practice aids, and any other activity features that may interest you.

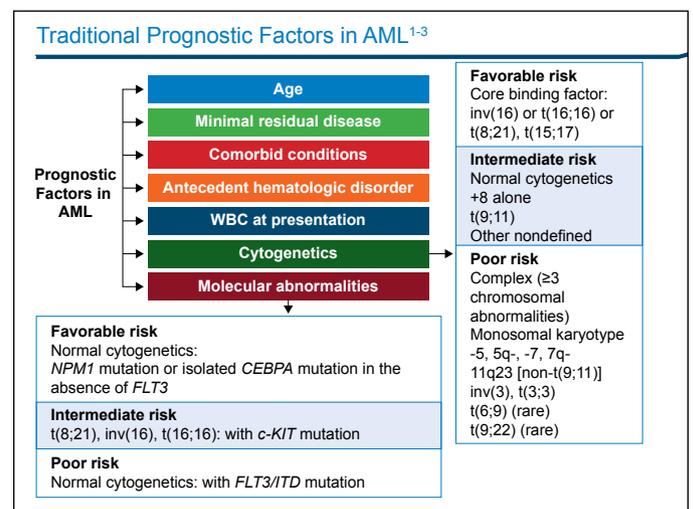


1. NCCN Clinical Practice Guidelines in Oncology. Acute myeloid leukemia. Version 2.2016.

Let's begin with diagnostic considerations for a newly diagnosed AML patient and what they mean for nurses. It's important to detail an accurate history, perform a physical examination, and evaluate for comorbidities. Other tests that can help establish a diagnosis and determine the AML subtype include a complete blood cell count with a differential, which, for example, can establish the level of leukocytosis. Other useful tests include a platelet count and chemistry profile; it's also important to look for coagulopathy, which is present in many leukemias, by evaluating PT, PTT, and fibrinogen.

AML is diagnosed by a bone marrow biopsy with aspiration, along with a cytogenetic and molecular analysis. If you think that your patient is a transplant candidate, HLA typing is critical before you wipe out the white blood cell count. For patients with symptoms of CNS involvement, you may need to perform a lumbar puncture to evaluate for CNS disease and a CT scan or MRI of areas of concern.

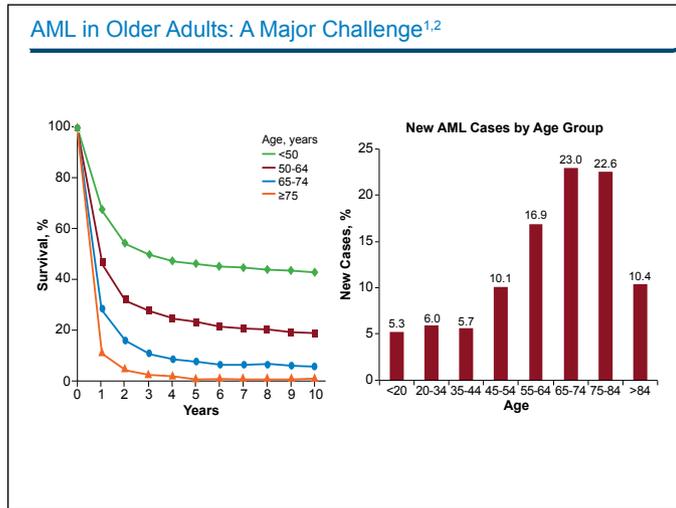
Before a patient receives anthracycline therapy, which is one of the mainstays of AML treatment, it's important to assess their myocardial function and ejection fraction, and also to assess for symptoms of cardiac disease prior to cardiotoxic therapies. Also, you would want to obtain from their health history whether they have had prior radiation therapy to the chest, which is often used for breast cancer treatment.



1. NCCN Clinical Practice Guidelines in Oncology. Acute myeloid leukemia. Version 2.2016.
2. Grimwade D, Hills RK. *Hematology Am Soc Hematol Educ Program*. 2009;385-395.
3. Estey EH. *Am J Hematol*. 2013;88:318-327.

Nurses need to consider prognostic factors before initiating treatment for AML. These include age; minimal residual disease, using flow cytometry and molecular markers; and evaluation of comorbidities that affect a patient's ability to tolerate induction chemotherapy. We should pose a few questions when making this assessment: Did they have antecedent hematologic disorder? Did they have myelodysplastic syndrome or a myeloproliferative neoplasm before they were diagnosed with AML? And what was the white blood cell count at presentation? A higher white blood cell count is more of a problem than leukopenia.

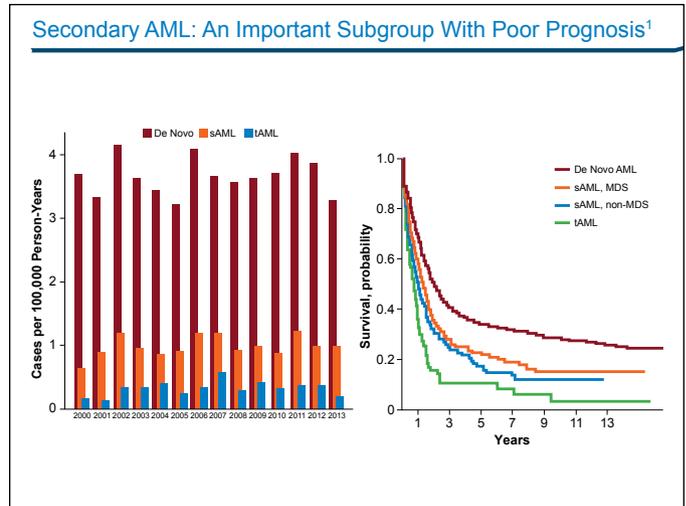
Another really important prognostic feature in evaluating AML is cytogenetics. We use three risk classes: favorable, intermediate, and poor risk. This risk determination guides our treatment decisions and whether we think a transplant is indicated, providing the patient is fit and otherwise healthy. And within the risk classes, we incorporate the molecular features of the disease and further classify patients, possibly changing their status from favorable to intermediate risk, for instance.



1. Surveillance, Epidemiology, and End Results (SEER) Program Populations. AML (1988-2012).
2. Surveillance, Epidemiology, and End Results (SEER) Program Populations. AML (2009-2013).

One of our major challenges is that AML is a disease of older patients. On the left side, you can see a Kaplan-Meier curve of survival in patients with AML; this is broken into four age groups. Patients aged 75 years and older were in the worst-performing group.

On the right, you can see the percentage of new AML cases by age group, with older patients being diagnosed most often. So, the group that does the most poorly is actually the one in which the majority of cases of AML occur. And that's really the problem—how do we best treat these older patients who have such an aggressive disease or life-limiting potential disease but are older and have comorbidities?



1. Granfeldt-Osgard, et al. *J Clin Oncol*. 2015;33:3641.

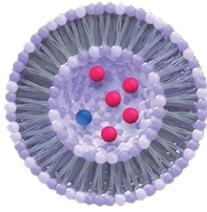
Secondary AML is an important subgroup with a poor prognosis. On the left, you can see secondary AML, in orange, and therapy-related AML, the blue bars. And you can see how those numbers play out in the cases per 100,000 person-years. On the right, you can see their probability of survival, and therapy-related AML is the worst player in this group.

**The Current State of AML: Therapy and Outcomes**

- AML is a highly heterogeneous disease with poor outcomes (particularly among older patients)
- Conventional therapies have largely remained unchanged for decades
  - Improvements in outcomes are mainly related to advances in supportive care
- Novel and effective therapeutic approaches highly sought after
  - Recently, for the first time, newer cytotoxic therapies have shown greater efficacy in some populations than has 7+3 chemotherapy

A highly heterogeneous disease, AML is associated with poor outcomes, particularly for our older patients, who are mostly likely to be diagnosed with AML. Although our conventional therapies really have not changed over the past decades, we have made improvements in outcomes. For the most part, these have been related to advances in supportive care. But now, we are excited to have novel and effective therapeutic approaches, including cytotoxic therapies, that have shown greater efficacy in some patients compared with the traditional 7+3.

### Cytarabine/Daunorubicin Liposome: CPX-351<sup>1</sup>



- 100-nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = cytarabine 1.0 mg plus daunorubicin 0.44 mg

CPX-351 recently tested in a phase 3 study vs 7+3 in patients with high-risk AML

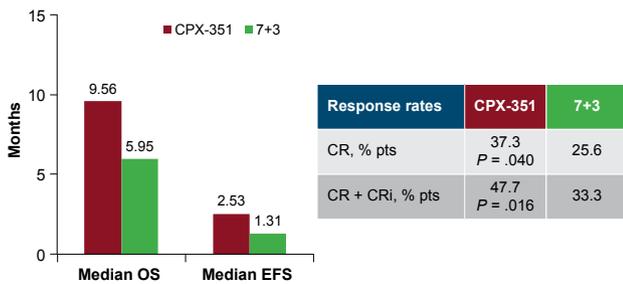
- Patients aged 60-75 years with treatment-related or secondary AML who were able to tolerate intensive therapy

1. Lancet JE et al. *Blood*. 2014;123:3239-3246.

One of those is the cytarabine/daunorubicin in a liposomal formulation known as CPX-351. This is a 100-nm bilamellar liposome. It was recently compared with 7+3 in a phase 3 study of patients with high-risk treatment-related or secondary AML who were aged 60 to 75 years.

### CPX-351 Versus 7+3 in Older Patients With Newly Diagnosed High-Risk AML: Efficacy Outcomes<sup>1</sup>

- CPX-351 improved outcomes vs 7+3 in all key efficacy parameters, including OS, EFS, and response



1. Lancet JF et al. 52nd Annual Meeting of the American Society of Clinical Oncology (ASCO 2016). Abstract 7000.

Looking at CPX-351 versus 7+3 in older AML patients who have high-risk disease, it was clear that CPX-351 improved the outcomes in all key efficacy parameters. You can see that median overall survival, event-free survival, and complete response rates were superior in the CPX-351 arm. Of note, the complete response rates with incomplete count recovery, or CRi—meaning that the patient has a complete response, but his or her platelet count is less than 100,000—was also superior.

### CPX-351 Versus 7+3: Grade 3-5 Nonhematologic AEs (Frequency ≥5%)<sup>1</sup>

MedDRA Preferred Term	CPX-351 (n = 153)	7+3 (n = 151)	All Patients (N = 304)
	n (%)	n (%)	n (%)
Febrile neutropenia	104 (68)	107 (71)	211 (69)
Pneumonia	30 (20)	22 (15)	52 (17)
Hypoxia	20 (13)	23 (15)	43 (14)
Sepsis	14 (9)	11 (7)	25 (8)
Hypertension	16 (10)	8 (5)	24 (8)
Respiratory failure	11 (7)	10 (7)	21 (7)
Fatigue	11 (7)	9 (6)	20 (7)
Bacteremia	15 (10)	3 (2)	18 (6)
Ejection fraction decreased	8 (5)	8 (5)	16 (5)

1. Lancet JF et al. ASCO 2016. Abstract 7000.

Let's take a look at the nonhematologic adverse events occurring with a frequency of 5% or greater. You can see that both the CPX-351 and 7+3 groups experienced fairly similar levels of adverse events. In addition, hypertension was greater in the CPX-351 group, at 10% versus 3%, and the patients in the CPX-351 arm were more likely than those in the 7+3 group to experience bacteremia at 10% versus 2%. The takeaway here is that the adverse events were similar between groups, with the exception being hypertension and bacteremia.

### CPX-351 Versus 7+3 in High-Risk AML: Count Recovery and Implications for Nurses<sup>1</sup>

#### Complete Recovery Counts for Patients Achieving CR or CRi

Parameters	ANC ≥500/μL		Platelets ≥50,000/μL	
	CPX-351	7+3	CPX-351	7+3
Patients receiving one induction, n	58	34	58	34
Median, d	35	29	36.5	29
Patients receiving two inductions, n	15	18	15	18
Median, d	35	28	35	24



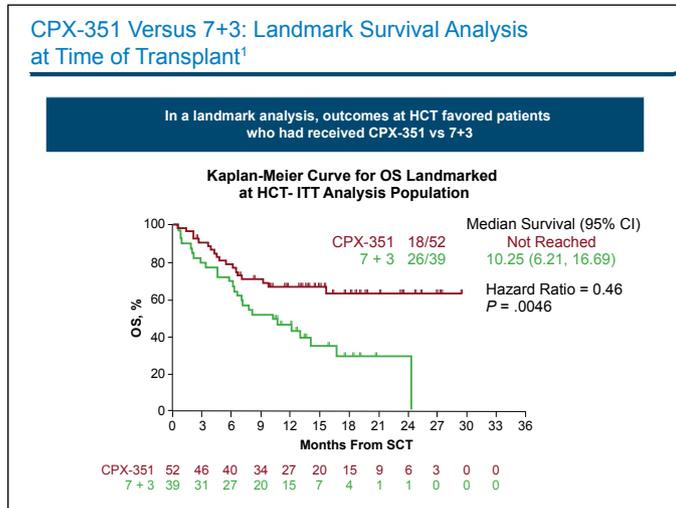
**Nurses: be prepared to manage prolonged cytopenias in patients with AML.**

1. Lancet JF et al. ASCO 2016. Abstract 7000.

What was really evident from the CPX-351 study was that patients experienced slower complete recovery of their blood counts than did their counterparts who were treated with 7+3. In particular, we looked at absolute neutrophil counts of at least 500 per microliter and platelet counts of at least 50,000 per microliter—key cutoffs for infection risk and bleeding events.

For patients having only one induction, the median recovery for ANC—or absolute neutrophil counts—was 35 days in the CPX-351 group versus 29 days in the 7+3 groups, with median platelet count recovery occurring at 36.5 days in the CPX-351 group and 29 days in the 7+3 group. Likewise, for patients who received two inductions, these counts improved more gradually in the CPX-351 group than in the 7+3 group. I'm going to turn to some other data from this study now, but later on we'll be discussing how the nurse can help manage these prolonged cytopenias.

In summary, based on the phase 3 data treatment with CPX-351, this agent is associated with improved overall survival, event-free survival, and response when compared with 7+3. Notably, these were patients with high-risk AML. The early mortality rates appeared lower in the CPX-351 arm, and both arms had comparable overall safety. And equally importantly, the survival outcomes following transplant favored CPX-351.



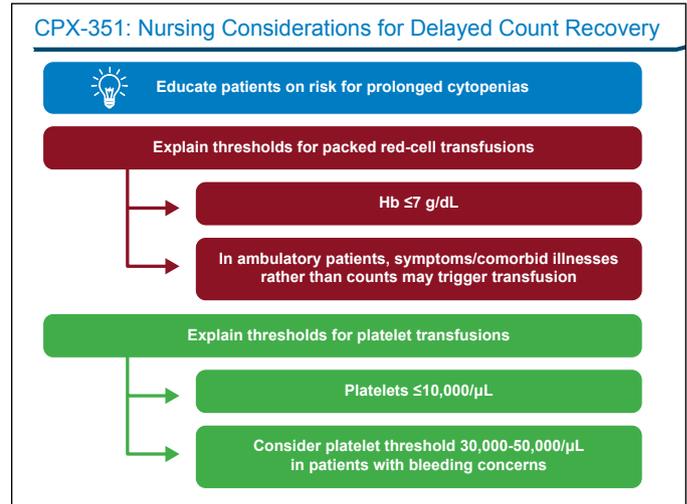
1. Lancet JF et al. ASCO 2016. Abstract 7000.

Outcomes from a landmark survival analysis at time of stem cell transplant also favored CPX-351 over 7+3. As shown in this Kaplan-Meier curve, the median overall survival has not yet been reached for the CPX-351 arm, whereas for 7+3, it was 10.25 months. And you can see that the hazard ratio associated with that was 0.46, so these data are very meaningful.

**CPX-351: Summary<sup>1</sup>**

- Based on phase 3 data, CPX-351 improved OS, EFS, and response vs 7+3 in patients with high-risk AML
- Early mortality rates appear lower in the CPX-351 arm; overall safety of CPX-351 comparable to that of 7+3
- Post-transplant outcomes favored CPX-351

1. Lancet JF et al. ASCO 2016. Abstract 7000.



So what does this mean for nurses? One issue I would like to focus on is how nurses can help manage prolonged cytopenias and help our older patients manage them, and how we can educate them on how to prepare for their potential emergence while on therapy.

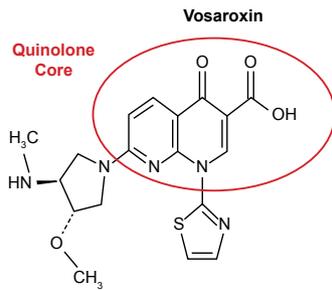
To begin with, it's important to understand the thresholds for transfusions with packed red blood cells or platelets in patients experiencing delayed count recovery. For hospitalized patients, we typically use a hemoglobin count of 7 g/dL or less as a threshold; however, for ambulatory patients, we really focus more on the symptoms and their comorbidities than a number when determining whether a transfusion is needed.

For example, we have patients in our clinic who have chronic obstructive pulmonary disease, coronary artery disease, or coronary heart disease and they may not be able to tolerate transfusions when they are given transfusion at a lower threshold. Instead, we may want to focus more on transfusing them when they're more symptomatic, using a cutoff, for example, of 8 g/dL. And for patients who are bleeding, we would use a higher threshold—a range of 30,000 to 50,000 per microliter—when determining whether a platelet transfusion is necessary. Patients with platelet counts of 10,000 per microliter or less are administered transfusions with platelets pretty regularly. And for patients who have this exceedingly low level of platelets, perhaps we need to bring them into the clinic more often, such as twice a week instead of once a week—until their platelet count recover to a safe range, and of course monitor them carefully for signs and symptoms of bleeding.

### Vosaroxin: A Novel Anticancer Quinolone Derivative

Lower potential for off-target damage (cardiotoxicity)<sup>1</sup>

Low risk of drug–drug interactions<sup>1</sup>



- Tested in phase 3 VALOR trial; N = 771; first relapsed or refractory AML<sup>2</sup>
- Randomized 1:1
  - Vosaroxin + cytarabine (vosaroxin + Ara-C)
  - PBO + cytarabine (PBO + Ara-C)

1. Freeman C et al. *Expert Opin Pharmacother.* 2013;14:1417-1427.  
 2. Ravandi F et al. *Lancet Oncol.* 2015;16:1025-1036.

Now, let's turn to vosaroxin, a novel anticancer quinolone derivative. You can see its structure on the right. What's really important is vosaroxin lowers the potential for off-target organ damage—or cytotoxicity—which is often associated with anthracyclines, as well as the risk of drug–drug interactions.

Vosaroxin was tested in the VALOR study. This was a phase 3 randomized, double-blind, placebo-controlled trial involving 771 patients with first-relapse or refractory AML. They were randomized one to one to vosaroxin plus cytarabine or placebo and cytarabine.

### Phase 3 VALOR Trial: Summary of Efficacy Outcomes<sup>1</sup>

No differences in median OS (primary endpoint), but improvements with vosaroxin in key secondary response endpoints noted

Secondary Endpoint	CR		CR + CRp + CRi	
	VOS + Ara-C	PBO + Ara-C	VOS + Ara-C	PBO + Ara-C
Overall	30.1%; P < .0001	16.3%	37.1%; P < .0001	18.6%
< 60 y	26.9%; P = .24	20.8%	34.6%; P = .04	23.1%
≥ 60 y	31.9%; P < .0001	13.8%	38.5%; P < .0001	16.0%
Early relapse	27.6%; P = .0024	12.4%	34.6%; P = .0004	15.5%
Late relapse	53.2%; P = .0148	33.8%	59.7%; P = .0037	36.4%
Refractory	20.4%; P = .0210	10.7%	27.6%; P = .0007	12.1%

1. Ravandi F et al. *Lancet Oncol.* 2015;16:1025-1036.

And there were no differences in median overall survival, which was the primary endpoint of the trial. However, there were improvements seen with vosaroxin in some key secondary endpoints. These included survival in patients aged 60 years and older, refractory AML, early relapse, and late relapse.

### VALOR: Safety and Summary<sup>1</sup>

- Early mortality similar between treatment groups
- More serious AEs noted in vosaroxin group vs cytarabine (33% vs 17%)
- Although primary endpoint not met, data from VALOR suggest that the addition of vosaroxin to cytarabine might be of clinical benefit to some patients with relapsed/refractory AML, including older patients

#### ≥ Grade 3 AEs More Frequent With Vosaroxin vs Cytarabine

Febrile neutropenia (47% vs 33%)
Neutropenia (19% vs 14%)
Stomatitis (15% vs 3%)
Hypokalemia (15% vs 6%)
Bacteremia (12% vs 5%)
Sepsis (12% vs 5%)
Pneumonia (11% vs 7%)



Be prepared to address safety considerations related to the use of vosaroxin in AML, particularly in older patients

1. Ravandi F et al. *Lancet Oncol.* 2015;16:1025-1036.

Many of the adverse events that were at least grade 3 occurring more frequently in the vosaroxin arm versus the cytarabine arm are common problems experienced by patients who are on active treatment for AML and included febrile neutropenia all the way down to pneumonia. As nurses, we have to be prepared to monitor our elderly patients for complications—particular infections, which we see most often—when receiving vosaroxin.

# Targeted Therapies for Patients With AML: Current and Future Directions

## Major Targets for Therapeutic Development in AML

- Many other novel therapies in development for AML, including antibodies and molecularly targeted agents

<b>CD33-targeting antibodies</b>	<ul style="list-style-type: none"> <li>• Gemtuzumab, vadastuximab (SGN-33A)</li> </ul>
<b>FLT3</b>	<ul style="list-style-type: none"> <li>• Many FLT3 kinase inhibitors explored in recent years; several next-generation agents in development (midostaurin, gilteritinib)</li> </ul>
<b>IDH</b>	<ul style="list-style-type: none"> <li>• Several inhibitors of IDH1/2 mutations in development for AML (AG-221)</li> </ul>
<b>Bcl-2</b>	<ul style="list-style-type: none"> <li>• Bcl-2 inhibitors established in CLL, now being tested in AML (venetoclax)</li> </ul>
<b>Nuclear export</b>	<ul style="list-style-type: none"> <li>• Selective inhibitors of nuclear export (SINE) in development for AML, including in combination with hypomethylating agents (eg, selinexor)</li> </ul>

Welcome back. Now we're going to move into a discussion of targeted therapies for patients with AML, including both molecularly targeted agents and antibodies targeting cell surface antigens. And we're going to focus on how the nurse can be prepared to manage patients who may soon be receiving treatment with these therapies. Several major targets for therapeutic development in AML include the CD33 antigen, FLT3, and IDH mutations; Bcl-2; and nuclear export.

## Gemtuzumab Ozogamicin and Other CD33-Targeting Antibodies

Gemtuzumab ozogamicin has demonstrated survival benefit in certain AML populations, but the incidence of VOD/SOS, as well as controversies regarding dosing and schedule, have limited its use<sup>1-10</sup>

Newer antibody-drug conjugates and bispecific agents (vadastuximab and AMG330, respectively) are being rapidly developed in AML



Be vigilant when managing patients with AML who are preparing for antibody treatment: monitor for infusion-related reactions, consider premedication prior to infusions, and monitor vital signs

1. Damle NK, Frost P. *Curr Opin Pharmacol*. 2003;3:386-390.
2. Sievers EL et al. *J Clin Oncol*. 2001;19:3244-3254.
3. Larson RA et al. *Cancer*. 2005;104:1442-1452.
4. McKoy JM et al. *Leukemia Res*. 2007;31:599-604.
5. Cohen AD et al. *Bone Marrow Transplant*. 2002;30:23-28.
6. Rajvansi P et al. *Blood*. 2002;99:2310-2314.
7. Petersdorf SH et al. *Blood*. 2013;121:4854-4860.
8. Castaigne S et al. *Lancet*. 2012;379:1508-1516.
9. Burnett AK et al. *Br J Haematol*. 2012;158:519-522.
10. Hills RK et al. *Lancet Oncol*. 2014;15:986-996.

So, let's talk about gemtuzumab ozogamicin and other CD33-targeting antibodies. Gemtuzumab has demonstrated survival benefit in certain AML populations. However, problems with veno-occlusive disease and controversies regarding dosing and schedule have limited its use. We now have newer antibody-drug conjugates, such as vadastuximab, and bispecific agents, including AMG330, that are being rapidly developed for AML. Overall, when treating patients with monoclonal antibodies, nurses have to be vigilant in looking for infusion-related reactions, with frequent monitoring of vital signs and premedication prior to infusions.

## Vadastuximab Plus HMA in AML: Efficacy<sup>1</sup>

- Anti-CD33 antibody-drug conjugate vadastuximab active in AML, including in combination with azacitidine or decitabine (based on a recent phase 1 study)

### Response Assessment per Investigator

Efficacy Evaluable	All N = 49	Adverse Cytogenetics Risk/MRC n = 18	Underlying Myelodysplasia n = 22
Remission Rate (CR + CRi)	71%	83%	73%
CR	41%	50%	32%
CRi (p)	18%	22%	32%

1. Fathi A et al. 21st Congress of the European Heart Association (EHA 2016). Abstract S503.

When vadastuximab was used in combination with azacitidine or decitabine in a recent phase 1 trial, the response rates were very encouraging. The remission rate was 71% for all patients, with the rates in the adverse cytogenetics and underlying myelodysplasia groups particularly impressive at 83% and 73%, respectively. And you can see the complete response rates for our adverse cytogenetic group at 50%. This is really exciting, as this patient population is typically difficult to treat.

### Vadastuximab + HMA in AML: Treatment-Emergent AEs in ≥20% of Patients<sup>1</sup>

Term	Incidence
Thrombocytopenia	53%
Febrile neutropenia	45%
Anemia	42%
Neutropenia	40%
Fatigue	57%
Nausea	49%
Constipation	42%
Peripheral edema	40%
Decreased appetite	40%
Diarrhea	30%
Pyrexia	30%
Dyspnea	25%
Vomiting	23%
Dizziness	21%
Headache	21%

- 30- and 60-day mortality rates, 2% and 8%, respectively
- No dose-limiting toxicities or infusion-related reactions observed
- 34% of doses delayed because of AEs, including
  - Neutropenia: 44%
  - Thrombocytopenia: 16%
  - Febrile neutropenia: 12%
  - Infection: 9%
  - Anemia: 5%
- No Grade 4 or 5 bleeding events observed

1. Fathi A et al. EHA 2016. Abstract S503.

You can see that the majority of adverse events occurring in at least 20% of patients treated with vadastuximab and hypomethylating agents in AML are the same as many of the side effects that can be seen in patients receiving commonly used therapies in AML, including hypomethylating agents or chemotherapy; these include events such as thrombocytopenia, anemia, GI symptoms, and headache.

Interestingly, there were no dose-limiting toxicities or infusion-related reactions with the vadastuximab-HMA regimen, and the 30- and 60-day mortality rates were 2% and 8%, respectively, with azacitidine or decitabine. In general, dose delays, which occurred in 34% of patients, were caused by cytopenias.

### Update on FLT3 Inhibitors in AML

<b>Sorafenib<sup>1,2</sup></b>	Addition of sorafenib to chemotherapy for FLT3-ITD AML improved survival in older adults, more than doubling the 1-y OS compared with historical controls (62% vs 30%; $P < .0001$ )
<b>Quizartinib<sup>3,4</sup></b>	As a single agent: 46%-57% response rate (CR + CRp + CRi) in relapsed/refractory AML
<b>Crenolanib<sup>5</sup></b>	As a single agent: 27% CR/CRi rate for patients resistant to other FLT3 TKIs

1. Chen YB et al. *Biol Blood Marrow Transplant*. 2014;20:2042-2048.
2. Uy GL et al. *Blood*. Abstract 319.
3. Levis MJ et al. 54th Annual Meeting of the American Society of Hematology (ASH 2012). Abstract 673.
4. Cortes J et al. ASH 2012. Abstract 48.
5. Galanis A et al. *Blood*. 2014;123:94-100.

Let's now move on to FLT3 inhibitors in AML. First, we're going to look at agents such as sorafenib, quizartinib, and crenolanib, before moving on to explore some other FLT3 inhibitors in more detail. In general, we have seen some intriguing data with these therapies; combining sorafenib with chemotherapy, for example, has improved survival in patients with FLT3-ITD AML, while single-agent quizartinib has been associated with high levels of response in relapsed/refractory disease. Finally, single-agent crenolanib has also been active in pretreated AML, with complete responses reported.

### Update on FLT3 Inhibitors in AML (Cont'd)

#### Midostaurin

- Phase 3 RATIFY study (7+3 induction midostaurin; N = 717 adults with newly diagnosed AML and FLT3 mutation)<sup>1</sup>

Outcome	Midostaurin	Placebo	P
Median OS, mo	74.7	26	.007
Median event-free survival, mo	8	3.6	.003
Allogeneic SCT at first remission, %	28	22	—

- Midostaurin had acceptable safety; no significant differences observed in overall rates of grade ≥3 hematologic and nonhematologic AEs
- 37 deaths occurred, with no difference in treatment-related deaths between the groups

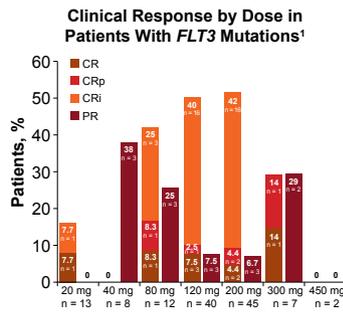
1. Stone R et al. ASH 2015. Abstract 6.

A newer FLT3 inhibitor, midostaurin was tested in the phase 3 RATIFY study, which looked at 7+3 as induction plus or minus midostaurin. You can see that patients in the midostaurin arm had superior response rates, including longer overall survival and event-free survival. Although the difference in allogeneic stem cell transplant at first remission was not statistically significant, there were improvements—28% versus 22%.

Midostaurin has an acceptable safety. No significant differences were observed in the overall rates of grade 3 or greater hematologic and nonhematologic adverse events. Unfortunately, there were 37 deaths, but no difference in treatment-related deaths was seen between the two groups.

Update on FLT3 Inhibitors in AML (Cont'd)

- Gilteritinib: potent, selective inhibitor of FLT3 and Axl with activity against FLT3-ITD and FLT3-TKD<sup>1</sup>
- Active at various dosages in phase 1/2 studies in relapsed/refractory AML
- Treatment-emergent AEs of any grade: diarrhea (13%), fatigue (12%), AST increase (11%), ALT increase (9%), decreased platelets (8%), and anemia (7%)
- Phase 3 studies planned



1. Levis M et al. 51st Annual Meeting of the American Society of Clinical Oncology (ASCO 2015). Abstract 7003.

Another next-generation FLT3 inhibitor, gilteritinib, is a potent selective inhibitor of FLT3 and Axl and has activity against FLT3-ITD and FLT3-TKD. It was active at various dosages in the phase 1/2 studies in the relapsed/refractory AML setting.

As for treatment-related adverse events of any grade, diarrhea, fatigue, increased AST and ALT, decreased platelets, and anemia occurred. Currently, there are several ongoing phase 3 studies of gilteritinib that should give us more information about the potential treatment role of this agent.

FLT3 Inhibitors for AML: Implications for the Hematology/Oncology Nursing Professional<sup>1,2</sup>



Watch for sensitivity in hands and feet  
• Consider using moisturizers

Watch for and manage GI events such as:

- Nausea
- Vomiting
- Diarrhea

As with any oral medication:

- Promote adherence to therapy
- Be mindful of potential drug–drug interactions

1. Stone R et al. ASH 2015. Abstract 6.  
2. Levis M et al. ASCO 2015. Abstract 7003.

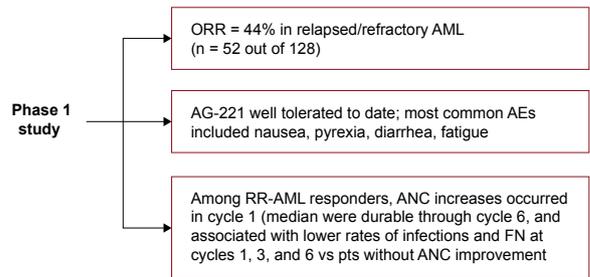
You may ask, “What does this mean for hematology and oncology nurses?” We need to watch for sensitivity or tenderness in the hands and feet, advising our patients to use moisturizers if any symptoms develop. We need to monitor for GI side effects, such as nausea, vomiting, and diarrhea, and administer antiemetics and antidiarrheals, as needed.

And, as with any other oral agent, we want to carefully monitor for adherence and encourage the patient to take the medication as prescribed. We also need to get an accurate medication list each time patients are seen in the clinic and advise patients to contact us if a new medication is added to their regimen so that we can check carefully for drug–drug interactions and then advise them accordingly.

“New Wave” of Therapy : IDH Inhibitors<sup>1</sup>

AG-221

First-in-class, oral, potent, reversible, selective inhibitor of the IDH2 mutant enzyme



AG-221 currently in phase 3 testing in AML

1. Stein EH et al. ASH 2015. Abstract 323.

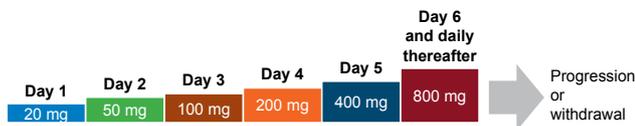
IDH inhibitors represent another wave of novel therapies that are being rapidly developed in AML. AG-221, for example, is a first-in-class oral potent reversible selective inhibitor of the IDH2 mutant enzyme. In a phase 1 study of patients in the relapsed/refractory setting, the overall response rate was 44%—or 52 of 128 patients. The exciting news about this drug class is that the therapy has been well tolerated, with most of the common adverse events gastrointestinal in origin, with some patients reporting pyrexia and fatigue.

And for the patients who responded in the relapsed/refractory setting, the ANC increases occurred in the first cycle and lasted through cycle 6 and were associated with lower rates of infections and febrile neutropenia at cycles 1, 3, and 6. This agent is in phase 3 testing in AML.

“New Wave” of Therapy: Bcl-2 Inhibition<sup>1</sup>

**Venetoclax:** Binds to and inhibits overexpressed Bcl-2; approved for use in relapsed/refractory CLL

**Phase 2 monotherapy study in AML**



- Venetoclax active as a single agent in subset of patients with AML
- Most common AEs of all grades in ≥20% of patients: nausea, diarrhea, and vomiting
- Most common grade 3/4 AEs occurring in ≥3 patients: febrile neutropenia and pneumonia

Response, n / %	N = 32
ORR	6 / 19
CR	2 / 6
CRi	4 / 13

1. Konopleva M et al. *Cancer Discov.* 2016;6:1106-1117.

Another new wave of therapy involves Bcl-2 inhibition. Approved for use in relapsed/refractory chronic lymphocytic leukemia, venetoclax works by binding to and inhibiting overexpressed Bcl-2. In a phase 2 study, patients with AML were treated with various doses of venetoclax until progression or withdrawal. This drug has demonstrated activity in a subset of patients with AML, with overall response rates of 19%.

The most common adverse events of all grades in at least 20% of patients were nausea, diarrhea, and vomiting. And febrile neutropenia and pneumonia were the most common grade 3 or 4 adverse events occurring in at least three patients.

So how should nurses prepare for using venetoclax? Clearly, we should anticipate tumor lysis syndrome, an issue that has been noted in the CLL experience. As such, we should perform a TLS risk assessment, ensure that the patient is adequately hydrated, and consider premedication with hyperuricemics prior to treatment. If necessary, nurses can help provide intravenous hydration; we should also be prepared to monitor electrolytes frequently and consider hospitalization for patients who are at high risk of or are showing signs of TLS. And, as with all AML patients, you want to continue to monitor for neutropenia and any signs or symptoms of infection and manage these issues as medically appropriate.

Selective Inhibitors of Nuclear Export: Selinexor

Patients with relapsed/refractory AML treated with oral selinexor (8-10 doses/4-week cycle) in one arm of a phase 1 trial in those with advanced hematological malignancies, including AML<sup>1,2</sup>

- Objective responses, reduction in blasts noted
- Most common grade 1/2 toxicities: nausea, anorexia, vomiting, fatigue, weight loss, and diarrhea

Phase 2 study showed selinexor in combination with cytarabine and idarubicin in relapsed/refractory AML with completed responses noted<sup>3</sup>

1. Savona M. ASH 2013. Abstract 1440.  
 2. Yee KWL et al. ASCO 2014. Abstract 7023.  
 3. Fiedler W et al. ASH 2015. Abstract 3789.

Another exciting drug that is in development is selinexor, a selective inhibitor of nuclear export. It is being used in patients with relapsed/refractory AML. Patients with advanced hematologic malignancies, including AML, received eight to ten doses of this oral agent in a 4-week cycle in one arm of a phase 1 trial. Patients did experience a reduction in blasts. The common grade 1 to 2 toxicities were gastrointestinal, and included nausea, anorexia, vomiting, diarrhea, weight loss, and fatigue. In addition, a phase 2 study showed that when used in combination with cytarabine and idarubicin, selinexor is active in the relapsed/refractory AML setting, with complete responses noted.

What the Nurse Needs to Know About Venetoclax<sup>1-3</sup>

**Based on CLL experience, anticipate TLS**

✓	Perform risk assessment in all patients
✓	Ensure adequate hydration, premedication with antihyperuricemics
✓	IV hydration, frequent monitoring, hospitalization as overall TLS risk increases



**Monitor for neutropenia; manage as medically appropriate**

1. Roberts AW et al. *N Engl J Med.* 2016;374:311-322.  
 2. Stilgenbauer S et al. ASH 2015. Abstract LBA-6.  
 3. Venclexta (venetoclax) prescribing information. <http://www.rxabbvie.com/pdf/venclexta.pdf>. Accessed November 18, 2016.

### Conclusions

- A modern understanding of the molecular features of AML has opened the door to the development of newer therapies with potential applications in many different treatment settings
- Novel cytotoxic agents will have a role in patient management and their use should be guided by evidence from clinical trials (eg, in older patients or those with high-risk AML)
- Targeted approaches range from anti-CD33 antibodies, newer FLT3 inhibitors, and innovative therapies targeting IDH, Bcl-2, or nuclear export
- Hematology-oncology nurse professionals have a vital role in educating patients with AML about these potential treatments and their adverse effects, managing safety issues, and offering emotional and logistical support

So in conclusion, our modern understanding of the molecular features of AML has opened the door to the development of newer therapies with potential application in many different treatment settings. We have novel cytotoxic agents that will have a role in patient management, and their use will be guided by evidence from clinical trials. We have targeted approaches ranging from anti-CD33 antibodies to newer FLT3 inhibitors and innovative therapies targeting IDH, Bcl-2, and nuclear export.

Hematology and oncology nurse professionals have a vital role in educating patients with AML concerning these potential new treatments and their adverse effects. Nurses are key in managing safety issues that may arise and offer emotional and logistical support to patients as they go through the AML treatment journey.



CE

# The Oncology Nurse's Role in AML Management: Focusing on the Patient in an Era of Novel Therapy

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**This activity is supported by an educational grant from Jazz Pharmaceuticals, Inc.**



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