What is secondary acute myeloid leukemia?

The term secondary acute myeloid leukemia (AML) refers to 2 separate entities. One type derives from antecedent hematologic malignancies, most commonly myelodysplastic syndrome (MDS), that progress to leukemia. The other type of secondary AML is related to therapy that patients received for other malignancies. Therapy-related AML is most often seen in patients treated with chemotherapy, but it can also develop after radiation.

The symptoms of secondary AML are similar to those of de novo acute leukemias. An exception is that secondary AML can be more indolent. Patients with secondary AML that develops from MDS may not have the sudden-onset illness typically associated with leukemia. Instead, the disease can manifest with slowly progressive fatigue, and perhaps some easy bruising and bleeding.

Patients with secondary AML have a poorer prognosis than those with other types of leukemia. Without bone marrow transplant, secondary AML is almost universally fatal. These subtypes tend to be associated with certain genetic and molecular abnormalities that have a poor prognosis. There are exceptions, however. Rare cases of therapy-related AML may exhibit a better genetic profile.

It is important to identify the particular subtype of AML. When a patient does not emergently need treatment, it is helpful to obtain a full panel of cytogenetic and next-generation sequencing studies to best characterize the disease and select the most appropriate therapy. Patients and practitioners often view acute leukemia as an emergency that requires immediate treatment. However, in some patients, especially those who had MDS that is now slowly progressing to AML, treatment can wait until the results of testing are available.

What are the treatment options for patients with secondary AML?

Until recently, there were not many therapies for these patients. The standard induction regimen, known as 7+3, consists of 7 days of cytarabine and 3 days of an anthracycline or an anthracenedione. In 2017, the US Food and Drug Administration (FDA) approved liposomal daunorubicin and cytarabine (Vyxeos, Jazz Pharmaceuticals) for the treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes (MRC). This treatment is now considered a standard of care for these patients who are fit enough to receive a more aggressive induction therapy. New options also include targeted therapies that can be added to aggressive regimens. For example, patients with secondary AML who are FLT3-positive can receive standard induction plus a FLT3 inhibitor.

Some patients with secondary AML are considered unfit for aggressive therapy. That is not to say they are unfit in general, but that they would benefit from treatment.
associated with fewer risks and complications. These patients are most commonly offered a hypomethylating agent plus venetoclax (Venclexta, AbbVie/Genentech), which in the AML setting is FDA-approved for the treatment of newly diagnosed disease in older patients (≥75 years) who cannot tolerate standard chemotherapy. Before the approval of venetoclax in this setting, patients were treated with a hypomethylating agent alone, and this strategy is still appropriate for patients who cannot tolerate the combination. Other possibilities for therapy include gemtuzumab ozogamicin (Mylotarg, Pfizer) in patients who are CD33-positive, and isocitrate dehydrogenase (IDH) 1 or 2 inhibitors for patients with IDH mutations. Another option is enrollment in a clinical trial, which should be considered for all patients in every population.

H&O What are the clinical trial data for liposomal daunorubicin and cytarabine?

MK The FDA approval of liposomal daunorubicin and cytarabine was based on a multicenter phase 3 study that compared this treatment with 7+3 standard induction therapy. The trial enrolled more than 300 patients, ages 60 to 75 years. Liposomal daunorubicin and cytarabine had a higher rate of complete response than standard induction therapy, at 37% vs 26%. This treatment was also associated with higher rates of overall survival. The rate of overall survival at 12 months was 42% with liposomal daunorubicin and cytarabine vs 28% with 7+3. At 24 months, these rates were 31% vs 12%, respectively. The majority of patients who did well were those who underwent transplant after treatment. The rates of patients who were able to proceed to transplant were 34% in the experimental arm vs 25% in the standard therapy arm. At 2 years posttransplant, nearly 70% of patients who received upfront liposomal daunorubicin and cytarabine were alive vs 30% of patients who received standard therapy.

H&O Which patients are appropriate candidates for liposomal daunorubicin and cytarabine?

MK The FDA approval is for patients with secondary AML, defined as either therapy-related AML or AML-MRC. However, increasing data suggest that it is possible to consider an expanded patient population. Trials presented at the 2019 American Society of Clinical Oncology meeting evaluated this treatment in older patients with all subtypes of untreated AML. The treatment was safe. In a trial of 30 older patients by Ritchie and colleagues, efficacy was at least as good (if not better) as in the original population studied. There are also ongoing trials in pediatric patients and relapsed/refractory patients.

Successful implementation of an outpatient approach requires that patients have quick, easy access to providers.

H&O How is liposomal daunorubicin and cytarabine administered?

MK Liposomal daunorubicin and cytarabine is administered in 1 or 2 induction doses followed by 1 or 2 consolidation doses. At my institution, we administer liposomal daunorubicin and cytarabine induction on an outpatient basis in some cases and to all patients receiving consolidation.

H&O What types of patients would you consider for outpatient administration?

MK Liposomal daunorubicin and cytarabine is a fairly intensive chemotherapeutic regimen. In general, patients who are candidates for liposomal daunorubicin and cytarabine are well enough to receive treatment as outpatients. Active, uncontrolled infections, which are fairly common among patients with leukemia, would prohibit treatment in the outpatient setting. Patients must be well enough to travel to our center. We require them to come in every day for the first 5 days, even though the infusion is administered on 3 days. On the 2 intervening days, we provide intravenous fluid support, transfusion support, and whatever else might be needed. After that first week, the patients come in twice a week. Typically, the patient must have a caretaker to help with travel. There is no specific requirement for how close the patient must live to our institution. When patients live far away, we sometimes help them arrange to stay near us for the first week of therapy, and then we ensure that they have a good cancer center closer to home to help with transfusion support. This center is typically one in our network that we work with on a regular basis.

H&O What type of institutional infrastructure support was needed to implement the outpatient approach?

MK The primary requirement was a commitment from
the advanced practice providers (APPs)—nurse practitioners and physician assistants—who provide most of the care for outpatients at our institution. Successful implementation of an outpatient approach requires that patients have quick, easy access to providers. Academic physicians are not in clinic every day, and therefore our availability to patients can be limited. We worked with APPs to establish the protocols for transfusion support, symptom management, and transfer of patients to the inpatient setting.

**H&O What is your experience with administering liposomal daunorubicin and cytarabine as outpatient therapy?**

**MK** Overall, the experience has been very positive. Patients are appreciative that they can avoid a stay in the hospital. There are fewer side effects with liposomal daunorubicin and cytarabine vs the traditional administration of 7+3. One exception, in my experience, is that infusion of liposomal daunorubicin and cytarabine is associated with more fevers than the 7+3 administration. It can be a complicated issue because when a patient becomes febrile, the first inclination is to admit him or her to the hospital. This is not always necessary. In our practice, when the fever appears to be related to the drug itself, we either continue outpatient administration or admit the patient to the hospital for a couple of days for observation.

In general, patients do well in the outpatient setting with liposomal daunorubicin and cytarabine infusion. At some point in the induction cycle, it is not uncommon for patients to develop a fever and require hospitalization. However, even if patients must be hospitalized at some point during the treatment course, they are still grateful to avoid the longer hospital stay required with planned inpatient administration.

**Disclosure**

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**Suggested Readings**


Cortes JE, Medeiros BC, Uy GL, et al. Outcomes by number of induction cycles with CPX-351 versus 7+3 chemotherapy in older adults with newly diagnosed, high-risk/secondary acute myeloid leukemia (sAML) [EHA abstract PF239]. *HemaSphere*. 2018;2(S1).


