Role of the Advanced Practitioner in the Management of Oral Chemotherapy for Adults With AML

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Abstract

Recent advances have resulted in an expansion of treatment options for AML, especially targeted therapies and low-intensity regimens. At JADPRO Live Virtual 2021, presenters reviewed novel and targeted oral chemotherapy for adults with AML and discussed multidisciplinary collaboration for patients with complex AML chemotherapy regimens.

Acute myeloid leukemia (AML) is the most common form of acute leukemia among adults and accounts for the largest number of annual deaths due to leukemias in the US. Recent advances in targeted therapies and low-intensity regimens, however, have resulted in an expansion of treatment options for patients with AML.

During JADPRO Live Virtual 2021, Ashley Leak Bryant, PhD, RN, OCN®, FAAN, UNC Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, and Kaitlyn Buhlinger, PharmD, BCOP, CPP, University of North Carolina Medical Center and University of North Carolina Eshelman School of Pharmacy, reviewed novel and targeted oral chemotherapy for adults with AML and discussed collaborative management of these complex regimens.

ORAL CHEMOTHERAPY CHALLENGES

With seven approvals since 2017, oral chemotherapy has shifted the treatment paradigm for patients with AML, expanding treatment options for those who would be ineligible for intensive chemotherapy and extending treatment into the relapsed setting (Figure 1). These new treatment options have also evolved care into the outpatient setting.

As more oral chemotherapies gain approval to treat AML, however, Dr. Bryant reported that adherence has become an issue. Findings of a focus group comprised of 100 patients with AML and their caregivers identified "the number of pills to be taken" as the most frequent and troublesome challenges associated with oral chemotherapies, and nearly 33% of patients indicated that they

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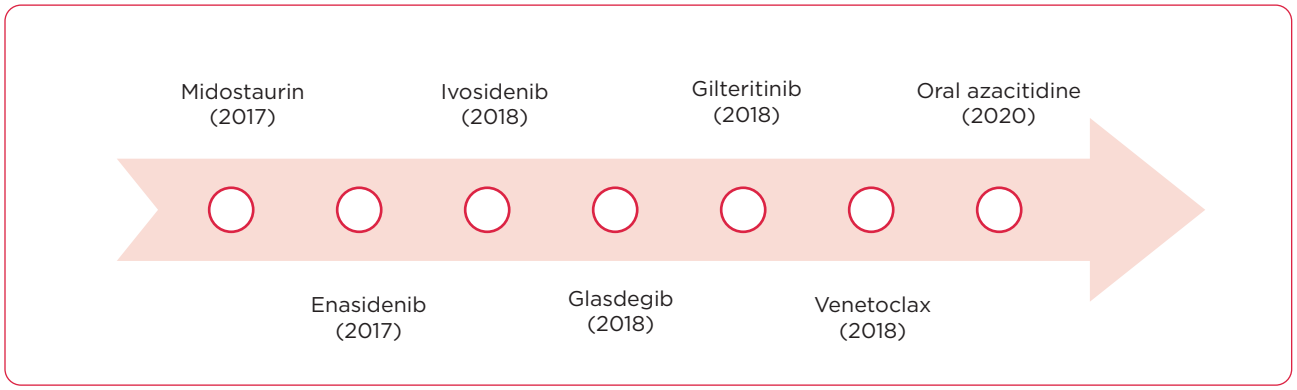

Figure 1. Recent leukemia oral chemotherapy approvals.

skip a dose altogether when they forget to take it (Bryant et al., 2020). The most frequently reported interventions that would improve patient adherence were smaller pills, easier packaging, and scheduling assistance, Dr. Bryant reported.

According to Dr. Buhlinger, the high cost of oral chemotherapy medications can also interfere with treatment. Unlike traditional chemotherapy that is on a hospital formulary, she said, many oral agents must pass through prior authorization to obtain prescription benefits, and copay assistance, including copay cards, grants, and manufacturer assistance, is important for uninsured patients.

"Financial toxicity is a real concern with these medications," said Dr. Buhlinger, who noted that oral chemotherapy can exceed $10,000 per month out of pocket, and copays can still cost thousands of dollars. "Time is of the essence when dealing with this disease, but it's important to make sure that these therapies are available for the patient at an affordable cost before proceeding with treatment."

IDH INHIBITORS

IDH mutations occur in approximately 20% of AML patients, with *IDH2* mutations occurring more frequently than *IDH1*. In the relapsed/refractory setting, two IDH inhibitors are available and used as oral monotherapy: ivosidenib (Tibsovo), which targets *IDH1*, and enasidenib (Idhifa), which targets *IDH2*.

Ivosidenib, which is dosed at 500 mg once daily, should not be administered with a high-fat meal as it could increase exposure and toxicity. Dr. Buhlinger also noted that patients should receive an electrocardiogram (EKG) at baseline, day 8, day 15, and then monthly to monitor for QTc prolongation. Because ivosidenib is a major CYP3A4 substrate, Dr. Buhlinger said that patients on strong CYP3A4 inhibitors such as posaconazole or voriconazole should dose reduce to 250 mg per day.

Enasidenib, which is dosed at 100 mg once daily, can be taken without regard to food. Gastrointestinal toxicities are the main adverse drug reactions and include issues with appetite and taste changes. Enasidenib also has moderate emetic potential, said Dr. Buhlinger, so patients should premedicate with 8 milligrams of ondansetron approximately 30 minutes prior to administration.

Finally, differentiation syndrome has been observed in 14% to 25% of patients on IDH inhibitors and can occur anywhere from days to months after initiation of therapy. Symptoms include fever, rash, pleural effusions causing shortness of breath, edema resulting in weight gain, and bone pain. Differentiation syndrome can also be detected with a high white blood cell count or acute kidney injury.

"If patients present with two or more of these symptoms, they should go to the emergency room, as steroids would need to be started immediately," said Dr. Buhlinger.

GILTERITINIB

FLT3 mutations occur in approximately 25% to 35% of patients with AML. Gilteritinib (Xospata), a dual inhibitor of *FLT3/AXL*, was approved in 2018 for relapsed/refractory *FLT3*-positive AML and is dosed at 120 mg once daily (3 × 40 mg tablets).

Patients receiving gilteritinib are monitored for QTc prolongation at baseline, day 1, day 8, day 15, and then monthly thereafter. According to Dr. Buhlinger, Fridericia formula for QT interval correction is more reliable than QTc readouts of an EKG.

Gilteritinib also has 3A4 metabolic implications, said Dr. Buhlinger, but no dosing adjustments are recommended. Patients on a 3A4 inhibitor, however, should be monitored with great frequency.

Differentiation syndrome is rare, but patients on gilteritinib are monitored weekly for 1 month, and then monthly.

ORAL AZACITIDINE

Oral azacitidine is approved for maintenance therapy in AML patients who are post-induction and/or consolidation and have achieved remission but are not transplant ineligible. Although that may sound straightforward, said Dr. Buhlinger, the application of oral azacitidine is somewhat more complicated, as transplant eligibility across institutions is variable and may be clinical and non-clinical in nature.

For those who are deemed eligible for treatment, oral azacitidine is dosed at 300 mg and is taken on days 1 to 14 of each 28-day cycle. Oral azacitidine is considered moderately emetogenic, so patients are premedicated with ondansetron (8 mg).

Complete blood counts should be checked for myelosuppression every 2 weeks for the first 2 cycles. Dr. Buhlinger also emphasized that oral azacitidine is not interchangeable with parenteral azacitidine.

"Importantly, oral azacitidine is NOT interchangeable with subcutaneous or intraveneous forms of azacitidine and should absolutely not replace this agent, particularly in the setting of low-intensity treatment, which is often combined with oral chemotherapy agents like venetoclax (Venclexta)," she said.

VENETOCLAX IN AML

A BCL2 inhibitor that induces leukemia cell apoptosis or cell death, venetoclax is approved for front-line AML in patients 75 years or older or patients who are deemed unfit for intensive chemotherapy. Expedited approval was based on phase I data in 2018, and phase III data published in 2020 confirmed an overall survival benefit.

Continuous oral venetoclax is combined with a hypomethylating agent (azacitidine 75 mg/m^2 × 7 days or decitabine 20 mg/m^2 × 5 or 10 days per 28-day cycle).

According to Dr. Buhlinger, venetoclax has been a "standard-of-care gamechanger in AML," but it's also a "complicated regimen" that requires multidisciplinary support.

"Venetoclax is often started inpatient at some institutions, but it can be done outpatient as long as there is structure and oversight," she said. "All of the AML agents we've discussed require a strong, outpatient, collaborative team approach for patient safety and the overall success of the regimen, but venetoclax-based regimens exemplify the need for multidisciplinary support" (Figure 2).

As Dr. Buhlinger explained, the actions surrounding venetoclax initiation revolve primarily around prevention of tumor lysis syndrome and the need to start treatment expeditiously. While rare in AML, tumor lysis syndrome can be life threatening if not carefully prevented and monitored, she said.

White blood cell count must be less than 25,000 prior to starting and may require cytoreduction with hydroxyurea (Palmer et al., 2021). Close laboratory monitoring for tumor lysis labs and chemistries must be done, particularly in the first several days of initiation when the risk of tumor lysis syndrome is at its highest.

"Patients are encouraged to hydrate extensively, and IV fluids are reasonable to add in the first several days of initiating," said Dr. Buhlinger. "Because a dose ramp-up is required to achieve a target dose of 400 milligrams, patients also need to be educated about how to self-administer this drug."

Venetoclax, which is a substrate of CYP3A4 and P-gp pathways, is also highly susceptible to drug interactions. Those interacting agents must be eliminated or replaced.

"Finally, because time is of the essence, an efficient and reliable medication assistance process must be in place to hasten access to venetoclax and avoid delays associated with treating AML in the outpatient setting," said Dr. Buhlinger.

INTERDISCIPLINARY COLLABORATION

Given the complexity of venetoclax-based regimens, significant interdisciplinary collaboration is required to keep patients safe and to achieve success. According to Dr. Bryant, multidisciplinary support of the patient and caregiver involves infusion staff, physicians, advanced practitioners, a leukemia pharmacist, a specialty pharmacist, nurse navigators, and a medication access specialist.

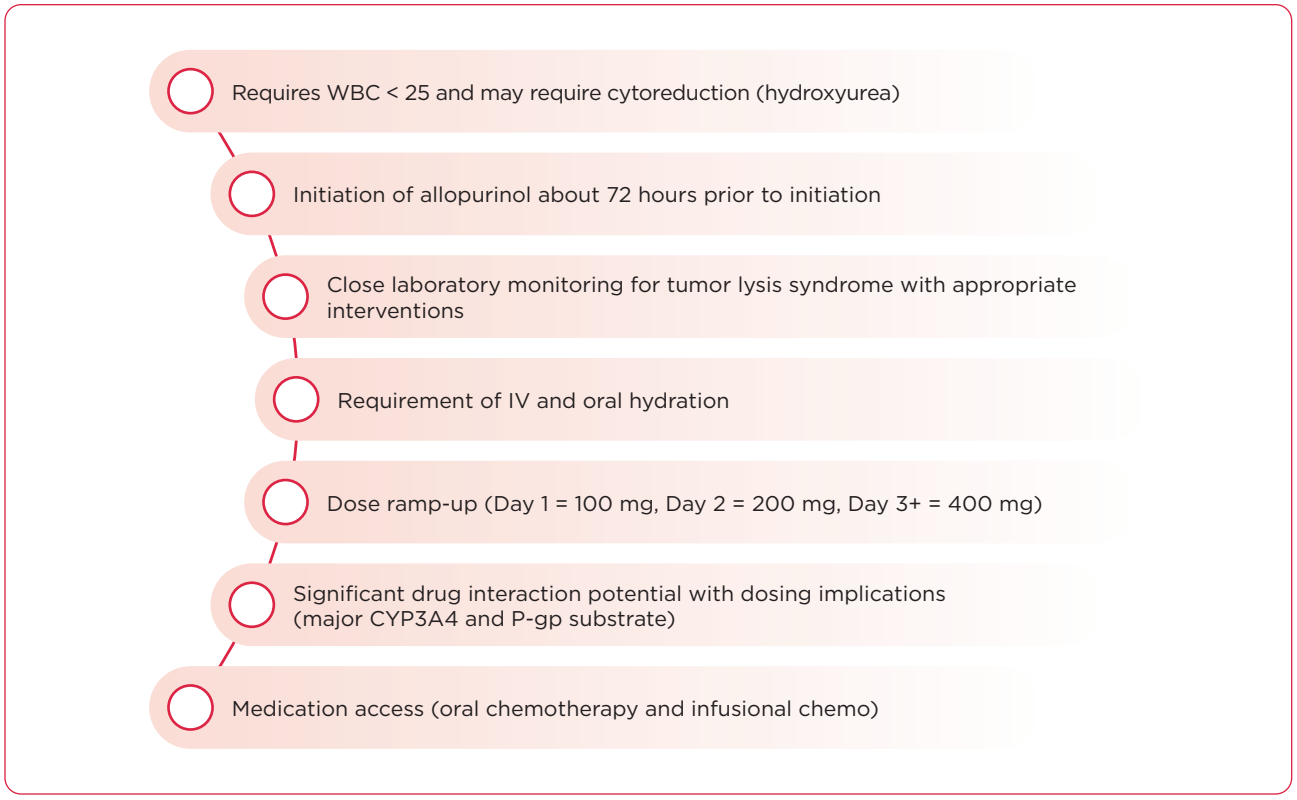

Figure 2. Venetoclax in acute myeloid leukemia. Information from Palmer et al. (2021).

At Dr. Bryant's institution, the program supporting venetoclax-based regimens is largely led by pharmacists. In addition to mitigating risk for tumor lysis syndrome and infection, interdisciplinary collaboration is required to manage physical and psychological symptoms, and there is a need to assess barriers to access, including transportation and financial toxicity.

"Our nurse navigators and others on the team are phenomenal in helping us think about what those barriers are and propose solutions," said Dr. Bryant.

"Consistent and constant closed-loop communication is another reason why we've been so successful," she added. "That ensures that the patient remains at the center of this conversation and that the medical team is in constant communication with each other."

As Dr. Bryant explained, patients return to the outpatient setting at least two times per week either for lab visits, transfusions, or in-person consultation with an oncologist or clinical pharmacist. Each one of these patient encounters is an opportunity to discuss adherence to medication, physical and psychological symptoms, and/or other concerns.

"It is a truly massive team effort, but it has been worth it, as we've been successful at keeping more than half of our AML venetoclax initiations outpatient," she said.

Disclosure

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