



Positive Quality Intervention: Venetoclax (Venclexta®) for the Treatment of Acute Myeloid Leukemia

Description: This Positive Quality Intervention will discuss the original approval of venetoclax for AML and practical management of select side effects.

Background: There are limited treatment options for elderly patients diagnosed with acute myeloid leukemia (AML) who are not eligible for intensive chemotherapy. Long term survival rates are only 10% due to a myriad of factors including poor performance status, increased risk of adverse-risk karyotypes, comorbidities and limited treatment options.¹ The FDA approved venetoclax in combination with a hypomethylating agent or low dose cytarabine for patients with newly diagnosed AML who are ≥ 75 years old or have comorbidities that make them ineligible for intensive chemotherapy based on VIALE-A and VIALE-C trials.^{2,3} VIALE-A was a phase III, placebo controlled trial of 431 patients with AML who were ineligible for standard induction chemotherapy due to comorbidities or were ≥ 75 years of age. 286 patients were randomized to the azacitidine 75 mg/m² IV for 7 doses + venetoclax 400 mg once daily group and 145 patients were in the azacitidine 75 mg/m² IV for 7 doses + placebo group. Overall survival was higher in the venetoclax group at 14.7 months (11.9 to 18.7 months) compared to 9.6 months (7.4 to 12.7 months) in the control group ($p < 0.001$). The composite complete remission (CR + CRi) was 66.4% in the venetoclax group vs 28.3% in the placebo group ($p < 0.001$). Hematologic adverse events (83% versus 69%) and infections (84% versus 67%) were both higher in the venetoclax group compared to the placebo group.² These results established venetoclax + hypomethylating agent as the standard of care for elderly or unfit patients. Tumor lysis syndrome (TLS) has been seen less with venetoclax in AML compared to CLL but still requires monitoring. Patients at increased risk for TLS include patients with renal impairment, high disease burden, dehydration, and baseline hyperuricemia. Preventative measures such as hydration and anti-hyperuricemics are recommended. Cytoreduction for patients with white blood cell counts (WBC) $> 25 \times 10^9/L$ should be performed prior to starting venetoclax. During the first cycle, there is also a venetoclax ramp up recommended over three days.⁴ Hematologic adverse events occurred in 83% of the VIALE-A participants and can result in infections and therapy delays.² Patients in the original phase 1b and the VIALE-A trials reported a median duration of neutropenia of 7-25 days throughout the first 5 cycles of treatment. Based on these results, patients who achieved a CR or CRi with delayed ANC recovery received 21 days of venetoclax per cycle instead of 28 days to facilitate count recovery.⁵ Venetoclax is a CYP3A4 and P-glycoprotein (P-gp) substrate and requires dose reductions when combined with moderate or strong inhibitors. Pharmacokinetic studies recommend a 75% dose reduction with strong CYP3A4 inhibitors such as voriconazole and 50% with moderate CYP3A4 inhibitors such as isavuconazole or fluconazole. When combined with a P-gp inhibitor a 50% dose reduction is advised.⁴

PQI Process:

- Upon receipt of prescription for venetoclax to treat AML, confirm the dosing and ramp-up schedule is appropriate for the indication
- Review concomitant therapies and recommend appropriate dose adjustments if interactions exist
- Ensure the WBC $< 25 \times 10^9/L$ prior to starting; if WBC $> 25 \times 10^9/L$, cytoreduction is recommended prior to starting venetoclax
- For patients with risk factors for TLS, additional measures such as increased laboratory monitoring, hospitalization, antihyperuricemic agents should be considered, as well as decreased starting dose
- TLS labs (including potassium, uric acid, calcium, phosphorus, and creatinine) should be monitored at baseline and 6 to 8 hours after the first dose/each dose increase
 - In select patients, rasburicase may be used for TLS (see [TLS Risk Assessment Tool](#) and [Use of Rasburicase \(Elitek®\) for Treatment of Tumor Lysis Syndrome PQI](#))

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Venetoclax Ramp-Up Schedule in AML	
Day 1	100 mg
Day 2	200 mg
Day 3	400 mg
Day 4 and beyond	400 mg with hypomethylating agent or 600 mg with low dose cytarabine

Coadministered Medication	Ramp Up Dose Modification	Steady Daily Dose Modification
Posaconazole	Day 1: 10 mg Day 2: 20 mg Day 3: 50 mg Day 4: 70 mg	70 mg
Other Strong CYP3A4 Inhibitors	Day 1: 10 mg Day 2: 20 mg Day 3: 50 mg Day 4: 100 mg	100 mg
Moderate CYP3A4 Inhibitors and P-gp Inhibitors	At least a 50% dose reduction is advised A modified ramp up schedule can be considered Day 1: 50 mg Day 2: 100 mg Day 3: 200 mg	200 mg

- See [Dose Modification Charts for Venetoclax Treatment Tool](#)
- Bone marrow assessment recommended at the end of Cycle 1 to measure response^{4,6}
 - After achieving remission, treatment should be delayed until counts recover

Patient-Centered Activities:

- Provide [Oral Chemotherapy Education \(OCE\)](#) Sheet
 - Do not chew, crush or break tablets
 - Take once daily with food and water
 - Confirm the titration schedule with the patient
- Confirm the patient is on a uric acid lowering agent 2-3 days prior to starting therapy and is staying adequately hydrated
- Review common adverse events like diarrhea, nausea or vomiting, fatigue, and lab abnormalities
- Patient Assistance: NCOA [Financial Assistance Tool](#)

References:

1. Samra B, Konopleva M, Isidori A, et al. Venetoclax-Based Complications in Acute Myeloid Leukemia: Current Evidence and Future Directions. *Front Oncol.* 2020;10:562558.
2. DiNardo CD, Pullarkat JV, Thirman JS, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *NEJM.* 2020;383:617-629.
3. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for Newly Diagnosed AML Ineligible for Intensive Chemotherapy: A Phase 3 Randomized Placebo-Controlled Trial. *Blood.* 2020;135(24):2137-2145.
4. [Venclexta® \[Venclexta\] package insert.](#)
5. Pratz KW, Wei AH, Pollyea DA, Jonas BA, Fiedler W, Recher C, et al. Management of Neutropenia during Venetoclax-Based Combination Treatment in Patients with Newly Diagnosed Acute Myeloid Leukemia. *Blood* (2019) 134(S):3897-7.
6. National Comprehensive Cancer Network Guidelines; https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf.