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VENETOCLAX-BASED LOWER-INTENSITY REGIMENS FOR ACUTE MYELOID LEUKEMIA: CLINICAL PEARLS FOR A NEW STANDARD OF CARE

Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease with variable genetic features and clinical outcomes. The main curative option for AML remains intensive chemotherapy and allogeneic hematopoietic stem cell transplant (HSCT) in selected patients.¹ However, with a median age at diagnosis of 67 years old and frequent comorbidities, a large proportion of patients diagnosed with AML are not eligible for intensive chemotherapy. Until recently, the only treatments available for patients with AML ineligible for intensive chemotherapy were single-agent hypomethylating agents (HMAs) such as azacitidine and decitabine, or low-dose cytarabine (LDAC).²⁻⁴ In older patients with AML, these treatments have been reported to improve outcomes over best supportive care (BSC) alone. However, in clinical studies the expected median overall survival (OS) remained less than 12 months. Fortunately, our increasing knowledge of AML biology has accelerated the development of novel targeted drugs for AML.⁵ Among these, the anti-apoptotic protein B-cell lymphoma 2 (BCL2) inhibitor venetoclax has completely changed the therapeutic landscape of AML, especially for patients who are ineligible for intensive chemotherapy. Venetoclax is approved by Health Canada for use in combination with azacitidine or LDAC for the treatment of newly diagnosed untreated AML in patients who are 75 years or older or have comorbidities precluding the use of intensive

chemotherapy. This approval is based on the two pivotal randomized, Phase 3 trials VIALE-A (azacitidine plus venetoclax) and VIALE-C (cytarabine plus venetoclax).^{6,7} Although seemingly easier to administer than intensive chemotherapy, venetoclax-based regimens are not as “non-intensive” as they are sometimes considered to be. They require the implementation of specific precautionary measures and monitoring to avoid excessive toxicity and optimize patients' outcomes (**Table 1**). We will review here practical points to safely administer venetoclax-based regimens to patients with AML who are ineligible for intensive chemotherapy.

Selection of Appropriate Patients

Defining eligibility for intensive chemotherapy can be challenging. We traditionally use patient-related factors associated with a high risk of severe complications or death during induction to define patients who are ineligible for intensive chemotherapy. The eligibility criteria used in the VIALE-A trial were age ≥ 75 years; symptomatic congestive heart failure (CHF) or left ventricular ejection fraction (LVEF) $\leq 50\%$; chronic stable angina; forced expiratory volume in 1 second (FEV1) or carbon monoxide lung diffusing capacity (DLco) $\leq 65\%$; and Eastern Cooperative Oncology Group (ECOG) performance status of 2 or 3.⁶ These criteria are used for funding of venetoclax in combination with azacitidine for newly diagnosed AML in patients ineligible for intensive chemotherapy.

In addition to patient-related factors, disease-related factors may weigh in the decision to select venetoclax-based lower-intensity regimens. Patients with adverse risk genetics (e.g., complex karyotype, monosomy 5 or 7, TP53 mutation) have poor response to intensive chemotherapy with complete remission (CR) rates of 30%-50%.⁸ Other factors such as an antecedent of hematological neoplasm such as myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN) and previous exposure to chemotherapy or radiotherapy (therapy-related AML) are also associated with lower rates of CR.⁹ In the presence of these adverse risk features, venetoclax-based lower-intensity regimens might be as effective as intensive chemotherapy to achieve CR, but with less toxicity. Therefore, lower-intensity regimens might be more suitable therapeutic options in somewhat older patients (60-75 years) or in those with non-severe comorbidities in whom the tolerance to intensive chemotherapy is uncertain, but the odds of achieving CR with intensive chemotherapy are low. Conversely, older patients or patients with comorbidities diagnosed with chemosensitive AML subtypes such as AML with inv(16)/t(16;16) or t(8;21) or with extramedullary disease, intensive chemotherapy with dose-adjustments as needed is likely the optimal treatment option.

An important exclusion criterion to highlight from the VIALE-A trial is the previous receipt of HMA or chemotherapy for prior history of MDS. These patients were, however, eligible to participate in the VIALE-C trial evaluating LDAC plus venetoclax. Unfortunately, patients with AML progressing from MDS following treatment with HMA or chemotherapy face a poor prognosis with a lack of approved, funded and effective therapies.¹⁰ Despite limited data in this subgroup of patients, the off-label addition of venetoclax to HMA or its use in combination with LDAC may help achieve remission and provide long-term benefit, especially in patients who can subsequently proceed to HSCT in remission.¹¹

Additional factors, such as the patient's preference and care objectives, distance from a leukemia referral centre to undergo induction chemotherapy, and subsequent potential eligibility for HSCT, are important to consider in the selection of frontline therapy for patients with AML.

Prevention of Tumour Lysis Syndrome

Venetoclax can cause tumor lysis syndrome (TLS) by rapidly inducing apoptosis of leukemia cells. The reported risk of TLS with venetoclax-based regimens in AML is approximately 1% to 5%; fortunately, clinically significant TLS with severe renal failure is rare.^{6,7} Risk factors for TLS include baseline chronic kidney disease (CKD); ongoing acute kidney injury (AKI); hyperleukocytosis (white blood cell count [WBC] $>50 \times 10^9/L$); and AML with *NPM1* and/or *IDH1/2* mutations which are more sensitive to venetoclax. It is important to note that the low reported

rates of TLS in clinical trials have been observed with the implementation of preventive measures for TLS which are described here (**Table 1**).

First, because TLS is associated with leukocytosis, the WBC count should be below $25 \times 10^9/L$ prior to initiating venetoclax-based regimens. Reduction of the WBC count can be achieved by hydroxyurea or by intermediate doses of cytarabine (500-1000 mg IV). Second, hydration is extremely important to prevent clinically significant TLS. In admitted patients, IV hydration with normal saline at 100 mL/h is a good strategy, but oral hydration of at least 2,000 mL per day is adequate in compliant patients. It is also important to address and control any baseline AKI prior to initiating venetoclax-based regimens and to avoid the administration of nephrotoxic medications. Third, all patients should be prescribed allopurinol prior to initial administration, and selected patients with spontaneous TLS or at high risk should be administered rasburicase. When prescribing rasburicase, typically I administer a single dose of 3 mg IV which can be repeated as needed depending on uric acid levels and the patient's condition. Last, venetoclax should be initiated at a low dose and escalated to the target dose over a few days to minimize the risk of TLS. In combination with azacitidine, recommended doses of venetoclax are 100 mg on Day 1; 200 mg on Day 2; and 400 mg on Day 3; and onwards (**Figure 1**). In combination with LDAC, a fourth day of ramp-up is added to achieve the target dose of 600 mg on Day 4. To monitor for TLS, it is recommended to perform blood work daily prior to each dose during the ramp-up period and 6 to 8 hours following the initial dose and each increased dose. In the VIALE-A and VIALE-C clinical trials, patients were required to be admitted for the venetoclax dose ramp-up to apply preventive measures and monitor closely for TLS. With the low occurrence of TLS in AML, it is reasonable to consider outpatient ramp-up for low-risk patients as long as the aforementioned preventive measures and monitoring for TLS can be implemented, and patients are compliant to oral hydration.¹²

Prevention of Infectious Complications

Infections remain one of the leading causes of mortality in patients with AML. In the VIALE-A trial, infections of any grade were more frequent with the combination of venetoclax plus azacitidine (84% vs 67%), as was the incidence of neutropenic fever (42% vs 19%). Conversely, the incidence of neutropenic fever was similar between patients treated with LDAC plus venetoclax or placebo in the VIALE-C trial (32% vs 29%). To reduce the risk of febrile neutropenia and infections in patients with AML, prophylactic antimicrobials with a fluoroquinolone for the prevention of bacterial infections, and acyclovir or valacyclovir for the prevention of herpes simplex virus (HSV) or varicella-zoster virus (VZV) infections, are recommended (**Table 1**).¹³

Prevention of tumour lysis syndrome

- Inpatient initiation in high-risk patients
- WBC $\leq 25 \times 10^9/L$ prior to initiating regimen
- IV hydration (NS 100 mL/h) or oral hydration (2,000 mL PO/day)
- Hypouricemic agents: Allopurinol for all and rasburicase in high-risk patients
- Venetoclax dose ramp-up (**Figure 1**)
- TLS blood work monitoring prior to and 6-8 hours following each new dose

Prevention of infectious complications

- Anti-bacterial prophylaxis (e.g., levofloxacin 500 mg PO daily)
- Anti-viral prophylaxis (e.g., valacyclovir 500 mg PO BID)
- Anti-fungal prophylaxis (e.g., posaconazole 300 mg PO daily)
- HBV re-activation prophylaxis as needed (e.g., entecavir 0.5 mg PO daily)
- Consider stopping anti-bacterial and anti-fungal prophylaxis when ANC $\geq 1.0 \times 10^9/L$

Response assessment and management of cytopenia

- BMA assessment at the end of cycle 1 (between Days 21 and 28) and at the end of every cycle until achievement of CR/Cri (complete remission with incomplete hematological recovery)
- Proceed with next cycle at day 29 if persistent disease
- Proceed with next cycle when ANC $\geq 1.0 \times 10^9/L$ and platelet count is $\geq 100 \times 10^9/L$
- Venetoclax duration reduction (21, 14 or 7 days) if persistent cytopenia ≥ 42 days
- Avoid delaying next cycle for more than 4 weeks
- Use G-CSF in patients with CR/Cri and mild/moderate neutropenia (ANC $> 0.5 \times 10^9/L$)

Venetoclax dose adjustments

- Dose reduction of 50% with moderate CYP3A4 inhibitors (e.g., fluconazole, isavuconazole, ciprofloxacin, diltiazem, etc.) – Target dose 200 mg with azacitidine
- Dose reduction of 75% with strong CYP3A4 inhibitors (e.g., posaconazole, voriconazole, ritonavir etc.) – Target dose 100 mg with azacitidine
- Avoid CYP3A4 inducers and use alternative medications

Table 1. Clinical pearls with venetoclax-based lower-intensity regimens; courtesy of Guillaume Richard-Carpentier, MD

Venetoclax dose ramp-up	Day 1	Day 2	Day 3+
No CYP3A4 inhibitor	 100 mg	 200 mg	 400 mg
Moderate CYP3A4 inhibitor (Fluconazole, Isavuconazole, Ciprofloxacin, Diltiazem)	 50 mg	 100 mg	 200 mg
Strong CYP3A4 inhibitor	 20 mg	 50 mg	 100 mg

Figure 1. Venetoclax initiation dose ramp-up with appropriate dose adjustments for concomitant administration of medications with CYP3A4 inhibition.

There are no randomized clinical trials evaluating the benefit of prophylactic antimicrobials in patients with AML receiving non-intensive regimens, however, the depth and duration of neutropenia (generally $<0.5 \times 10^9/L$ for >7 days) observed with venetoclax-based regimens justifies their use. For bacterial prophylaxis, I prefer levofloxacin because of its daily administration and absence of CYP3A4 inhibition in contrast to ciprofloxacin. Unfortunately, invasive fungal infections are frequent in patients treated with venetoclax-based regimens, with one clinical study reporting a rate of 12.6%.¹⁴ Therefore, antifungal prophylaxis with a triazole with anti-mold activity (posaconazole, voriconazole or isavuconazole) is also recommended.^{13,15} Unfortunately, because of the elevated cost and restrictive funding criteria for these drugs, anti-mold triazoles for prophylaxis of aspergillosis in patients with AML are not accessible in all jurisdictions. At the least, fluconazole may prevent oropharyngeal or esophageal candidiasis and candidemia in these patients. Importantly, azole antifungals are CYP3A4 inhibitors and dose adjustments for venetoclax are required when these drugs are administered concomitantly as described below (**Figure 1**). Patients at risk of hepatitis B virus (HBV) reactivation (anti-HBc positive) should also receive a nucleoside reverse transcription inhibitor (e.g., entecavir or tenofovir). Prophylaxis for *Pneumocystis jirovecii* is not routinely recommended but might be considered in patients with additional risk factors.

In summary, I prescribe triple prophylaxis with levofloxacin, posaconazole and valacyclovir in patients treated with venetoclax-based lower-intensity regimens which I continue until they achieve remission (**Table 1**). Once in remission with neutrophils $\geq 1.0 \times 10^9/L$, I typically continue valacyclovir and hold anti-bacterial and anti-fungal prophylaxis as long as episodes of neutropenia, if any, are brief (<7 days) and non-severe.

Monitoring of Response and Management of Cytopenia

The addition of venetoclax to LDAC or azacitidine is associated with higher rates of severe and prolonged cytopenia. During the first cycle, I monitor complete blood counts (CBC) twice weekly as the majority of patients require transfusions. At the end of cycle one of azacitidine plus venetoclax, most patients will have absolute neutrophils count (ANC) $<0.5 \times 10^9/L$ and platelets $<50 \times 10^9/L$. Therefore, it is critical to perform a bone marrow aspiration (BMA) and biopsy at the end of the first cycle to evaluate if the cytopenia is related to persistent disease or to the effect of treatment. Approximately 50% of patients who achieve remission with venetoclax-based regimens will do so after the first cycle and others generally after the second cycle. Typically, I perform the end of cycle one BMA around Day 21 in order to know by Day 28 if patients have achieved morphological remission ($\leq 5\%$ bone marrow blasts.) In patients with persistent disease, it is

recommended to proceed with a second cycle without waiting for count recovery. In patients with remission, but without complete count recovery (ANC $<1.0 \times 10^9/L$ and/or platelets $<100 \times 10^9/L$), it is recommended to wait for count recovery prior to proceeding with cycle two. In these situations, I stop the venetoclax whenever I obtain the BMA results even if the patient has not completed 28 days of treatment. When ANC recovers i.e., $\geq 1.0 \times 10^9/L$ and the platelet count is $\geq 100 \times 10^9/L$ within two weeks following the end of the cycle (Day 42), patients can proceed with the next cycle without dose adjustments. In patients with some degree of count recovery with ANC $\geq 0.5 \times 10^9/L$ and a platelet count of $\geq 50 \times 10^9/L$, I typically proceed with the next cycle, with adjustment of the duration of venetoclax to 21 days or 14 days, depending on the duration of the previous cycle. In patients with no count recovery beyond 42 days, I repeat a BMA to reassess if the leukemia is not in remission or if bone marrow aplasia is persistent. In patients with persistent aplasia without count recovery, I proceed with a next cycle of treatment after delaying a maximum of 3 to 4 weeks. In these circumstances, I adjust treatment by decreasing the duration of venetoclax to 7 or 14 days and sometimes azacitidine to 5 days instead of 7 days. In patients with persistent cytopenia, relapse is almost guaranteed without treatment for a prolonged period. On subsequent cycles, I apply the same algorithm, proceeding to the next cycle whenever ANC recovers $\geq 1.0 \times 10^9/L$ with a platelet count of $\geq 100 \times 10^9/L$ (or at least ANC $\geq 0.5 \times 10^9/L$ and platelets $\geq 50 \times 10^9/L$) without dose adjustments if cycle lengths are less than 42 days. Additionally, I decrease the duration of venetoclax if cytopenia persists beyond 42 days. Despite the fact that the VIALE-A and VIALE-C clinical trials had planned protocols for continuous administration of venetoclax, the majority of patients will generally receive venetoclax for 14 to 21 days on steady-state and have a cycle duration of approximately 5 weeks. Post-hoc data from these trials have shown that patients with these adjustments have similar outcomes vs those who can proceed with treatment without modifications and delays. Filgrastim (G-CSF) can be administered without any concerns in patients with mild-to-moderate neutropenia after achieving complete remission. I use it in patients who have been able to spontaneously recover neutrophils in previous cycles and who are on a stable duration of venetoclax and cycle length. Depending on patients' blood counts and the risk of relapse based on genetic features, I repeat BMA every 3 to 6 cycles or whenever there are new, significant cytopenias suggestive of relapse. If patients relapse after an initial response, I sometimes re-increase the duration of venetoclax to 28 days and azacitidine to 7 days in an attempt to salvage their response or at least stabilize their disease while considering alternative therapies, if any are available.

Venetoclax dose adjustments

Venetoclax is metabolized by CYP3A4 and concomitant administration of CYP3A4 inhibitors or inducers will affect the plasma concentration of venetoclax. Therefore, dose adjustments are warranted in patients receiving pharmaceuticals that alter CYP3A4 metabolism in order to avoid excessive toxicity, especially severe and prolonged myelosuppression (**Table 1**). Strong CYP3A4 inhibitors such as posaconazole, voriconazole and ritonavir require venetoclax dose reduction of 75% to 90%.¹⁶ Therefore, patients treated with venetoclax in combination with azacitidine should start the ramp-up with venetoclax 20 mg on Day 1; 50 mg on Day 2; and 100 mg on Day 3 and onwards, with some data even suggesting a steady dose of 70 mg of venetoclax with concomitant administration of strong CYP3A4 inhibitors, especially posaconazole (**Figure 1**). With moderate CYP3A4 inhibitors such as ciprofloxacin, fluconazole and diltiazem, the venetoclax dose should be adjusted to 50% of the target dose. Therefore, in combination with azacitidine, venetoclax should be administered at a dosage of 50 mg on Day 1; 100 mg on Day 2; and 200 mg on Day 3 and onwards with a moderate CYP3A4 inhibitor (**Figure 1**). As mentioned above, I prefer levofloxacin for anti-bacterial prophylaxis because the additive effect of ciprofloxacin with a triazole anti-fungal on CYP3A4 inhibition is unknown and informed recommendations for venetoclax dose-adjustments cannot be made. Grapefruit, starfruit and Seville oranges also contain a CYP3A4 inhibitor and should be avoided by patients taking venetoclax. CYP3A4 inducers such as carbamazepine, phenytoin or rifampin should be avoided as they may decrease the clinical effect of venetoclax. Alternative drugs should be utilized instead.

Conclusion and Future Perspectives

The addition of venetoclax to lower-intensity regimens has significantly changed the therapeutic landscape for patients with newly diagnosed AML who are ineligible for intensive chemotherapy. These regimens improve remission rates and overall survival over single-agent LDAC or HMAs, but require specific monitoring measures to minimize the risk of complications and optimize patients' outcomes (**Table 1**). Specific measures include hydration, hypouricemic agents, prior cytoreduction, and venetoclax dose ramp-up to decrease the risk of TLS; infectious prophylaxis to prevent neutropenic fever episodes and infections; and venetoclax dose-adjustments to manage drug interactions. The time to response (TTR) is also more rapid with venetoclax-based lower-intensity regimens vs single-agent LDAC or HMA. Performing a bone marrow assessment following the first cycle and periodically thereafter is critical to determine if the cytopenia is related to relapsed or refractory leukemia, or to treatment effect, and to subsequently manage the cytopenia appropriately. Despite providing better outcomes for patients who are ineligible for intensive chemotherapy, approximately

one-third of patients will not achieve remission with these regimens and the majority of patients achieving remission will nonetheless eventually relapse. Thankfully, the future holds promise for patients with triplet combination regimens including FLT3, IDH1/2 inhibitors or monoclonal antibodies being evaluated to further improve efficacy and outcomes in this patient population.

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