

Management guide for treatment with venetoclax and azacitidine in patients with acute myeloid leukemia ineligible for intensive chemotherapy

Guía de manejo del tratamiento con venetoclax y azacitidina de pacientes con leucemia mieloblástica aguda no tributarios de quimioterapia intensiva

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Abstract

Acute myeloid leukemia (AML) is a disease with poor prognosis, characterized by significant clinical and biological heterogeneity. Although the genetic diversity of AML has been recognized for over 30 years, recent advancements in gene sequencing have uncovered its complex molecular landscape, identifying clinical mechanisms and recurrently implicated genes driving its pathogenesis. This enhanced understanding has facilitated the development of risk-adapted therapies, which, combined with improvements in supportive care and hematopoietic stem cell transplantation (SCT), have increased the cure rates to approximately 50% in younger patients. However, this progress has not been mirrored in older patients or those with comorbidities, who are ineligible for intensive chemotherapy or SCT. In recent years, the VIALE clinical trials, which evaluate the combination of venetoclax with low-dose cytarabine or azacitidine, have demonstrated promising outcomes. Notably, the VIALE-A phase III trial demonstrated that combined venetoclax with azacitidine significantly improved overall survival, with a median of 14.7 months compared to 9.6 months observed with azacitidine as single agent. These findings have changed the therapeutic approach for these patients, leading the CETLAM (Grupo Cooperativo de Estudio y Tratamiento de las Leucemias Agudas y Mielodisplasias) group to develop a consensus guideline for their management.

Keywords: Acute myeloid leukemia. Venetoclax. Azacitidine. CETLAM.

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Resumen

La leucemia mieloide aguda (LMA) es una enfermedad con pronóstico desfavorable, caracterizada por su heterogeneidad clínica y biológica. Aunque la diversidad genética de la LMA se conoce desde hace más de 30 años, los avances recientes en secuenciación génica han revelado una compleja heterogeneidad molecular, identificando mecanismos y genes recurrentemente implicados en su desarrollo. Este mayor conocimiento ha permitido diseñar terapias adaptadas al riesgo, lo que junto con mejoras en el tratamiento de soporte y en el trasplante de progenitores hematopoyéticos (TPH), ha aumentado la tasa de curación hasta un 50% en pacientes jóvenes. Sin embargo, este progreso no se refleja en pacientes mayores o con comorbilidades, quienes no son candidatos a quimioterapia intensiva ni a TPH. Recientemente, los ensayos clínicos VIALE, que combinan venetoclax con dosis bajas de citarabina o azacitidina, han mostrado resultados prometedores. Específicamente, el ensayo fase III VIALE-A demostró que la combinación de venetoclax y azacitidina mejora significativamente la supervivencia global, alcanzando una mediana de 14,7 meses frente a los 9,6 meses observados con azacitidina en monoterapia. Estos hallazgos han modificado el tratamiento de estos pacientes, lo que ha motivado al grupo Grupo Cooperativo de Estudio y Tratamiento de las Leucemias Agudas y Mielodisplasias (CETLAM) a desarrollar una guía de consenso para su manejo.

Palabras clave: Leucemia mieloide aguda. Venetoclax. Azacitidina. CETLAM.

Introduction

The incidence rate of acute myeloid leukemia (AML) increases with age, with a median age at diagnosis of 68 years in our environment¹. In turn, tolerance to standard treatment, based on intensive chemotherapy with anthracyclines and cytarabine (3+7), progressively decreases with age². Due to this lower tolerance and efficacy, older patients often receive less aggressive therapies. However, an exception to this trend are patients with favorable-risk AML, according to the European LeukemiaNet (ELN) 2022 prognostic classification³. In this subgroup, intensive treatment can offer acceptable rates of overall survival (OS) and event-free survival (EFS), and even the possibility of cure^{4,5}. Unfortunately, the rate of favorable prognosis cytogenetic and molecular alterations in older patients is very low.

Within the Cooperative Working Group for the Study and Treatment of Acute Leukemias and Myelodysplasias (CETLAM), the response rate and the probability of 1-year OS of favorable-risk AML patients on the 2 therapeutic strategies (n = 34), intensive (CETLAM 2012, n = 17) and non-intensive (CETLAM 2016, n = 17)⁶, were analyzed. When comparing the probability of 1-year OS based on the treatment received, it turned out to be 32% (95% CI. 8-56%) in the non-intensive treatment group vs 94% (95% CI, 83-100%) in the intensive treatment group (p < 0.001). Based on these results, the CETLAM continues to recommend the intensive alternative for these patients, following an individualized assessment to determine their eligibility based on objective evaluation criteria and scales

(Hematopoietic Stem Cell Transplant-Comorbidity Index [HCT-CI] and Ferrara Criteria)^{7,8}.

The prognosis of AML patients older than 70 years is very unfavorable. On the one hand, these are individuals who frequently present comorbidities and have poorer tolerance to intensive chemotherapy, with periods of prolonged neutropenia. On the other hand, AML *per se* in elderly patients more frequently presents unfavorable prognostic characteristics (trilineal dysplasia, poor prognosis cytogenetic and molecular alterations, treatment-related or other myeloid neoplasm-related leukemias, and resistance to cytostatics)^{9,10}. For these reasons, the treatment of patients not eligible for intensive chemotherapy is a challenge and a subject of constant research. We must always keep in mind that this is an ideal population for inclusion in clinical trials.

In 2015, low-intensity treatments with hypomethylating agents (HMA) such as subcutaneous (SC) azacitidine (AZA) and intravenous (IV) decitabine were approved in Europe. These agents demonstrated a low toxicity profile (induction mortality < 10%) with median OS from 7 to 10 months across different studies¹¹⁻¹³. Compared to other attenuated chemotherapy regimens (e.g., FLUGA [fludarabine and cytarabine]), the AZA regimen was superior regarding OS in the FLUGAZA clinical trial, which compared the 2 therapeutic strategies (1-year OS probability of 47% vs 27% and median OS of 9.8 vs 4.1 months; p = 0.005)¹⁴. Despite this, the short survival of patients not undergoing intensive treatment and the improvement in supportive care treatments, including growth factors, antibiotics, and antifungals, has increased the trend to seek slightly

more intensive therapeutic approaches in this population with such a poor prognosis.

In 2020, after a long period of seeking to improve the results of HMA treatment through combination with other agents, the results of the VIALE-C¹⁵ and VIALE-A¹⁶ clinical trials were published. These trials combined venetoclax (an oral anti-BCL2 agent) with low doses of cytarabine or AZA and demonstrated the superiority of the combination vs AZA monotherapy in terms of complete remission (CR) rate and OS probability. These results have led to a change in the therapeutic approach for patients not candidates for intensive chemotherapy¹⁷.

The objective of this work is to provide a management guide for the care treatment using the venetoclax plus AZA (VENAZA) regimen in patients ineligible to receive intensive chemotherapy with a recent diagnosis of AML (de novo or secondary).

Population covered by this guide

This guide is aimed at previously untreated AML patients (de novo or secondary) who are ineligible to receive intensive chemotherapy. Cases with AML with t(15;17), acute biphenotypic leukemia, or blastic crisis of chronic myeloid leukemia are excluded. Although these are mostly elderly patients, the therapeutic strategy should be individualized according to the frailty profile, and not based solely on chronological age. The reference method for this classification is the Comprehensive Geriatric Assessment (CGA), a multi-dimensional and validated tool that allows predicting toxicity and non-cancer-dependent prognosis, supporting therapeutic decisions in multidisciplinary teams, and implementing adapted geriatric interventions^{18,19}. However, the systematic implementation of CGA is difficult in many centers due to the need for specific resources (space, time, and specialists). As alternatives, the following are proposed:

- Frailty screening tools, such as G8 or VES-13, which allow identification of which patients require a more complete assessment²⁰⁻²³.
- Basic geriatric assessment instruments, which are shorter and applicable by non-geriatric professionals within the available care time²³.

Treatment description

Treatment is based on the combination of venetoclax and AZA, according to the phase III VIALE-A study, and must be initiated and supervised by a hematologist experienced in acute leukemia.

- AZA is administered at 75 mg/m² IV or SC, on days 1-7 or in an outpatient 5-2-2 regimen (Monday to Tuesday of the following week, with rest on the weekend). When administered SC, injection sites should be rotated (thigh, abdomen, upper arm), applied at least 2.5 cm from the previous location. In patients where the SC route is not convenient, it can be administered IV. Antiemetic treatment will be required prior to administration (ondansetron 8 mg oral [PO] 1 hour before AZA administration is recommended). AZA down titration will be recommended based on the technical specifications²⁴, after the 3rd cycle of VENAZA treatment, in case of prolonged cytopenias despite venetoclax dose reduction and addition of granulocyte colony-stimulating factors (G-CSF).
- Venetoclax: Venetoclax administration during cycle 1 (C1) requires up titration (Fig. 1) and should preferably be done at night (00:00 h) to allow monitoring for tumor lysis syndrome (TLS) (morning blood work will serve as a control 8 h post-administration). Venetoclax tablets can be 10 mg, 50 mg, or 100 mg and should be administered once daily with food. The tablets must be swallowed whole with a glass of water; do not crush, break, or chew²⁵. In special situations where swallowing is not possible, the drug can be diluted in sterile water for injection, under the supervision of the pharmacy department, and administered via a nasogastric tube.

Given the risk of TLS, it is essential to assess the risk, establish prophylactic measures (such as initial hospitalization or close monitoring), adjust doses, and perform analytical controls. As it is metabolized by the CYP3A cytochrome, venetoclax requires dose adjustment if administered with moderate or potent inhibitors of this enzyme to reduce the risk of TLS and other toxicities. It also interacts with P-gp inhibitors. Although concomitant use is discouraged, if there is no alternative, it is recommended to down titrate venetoclax by 50% and closely monitor toxicities. It is always recommended to review the medication with the pharmacy department to identify potential interactions. Patients should consult their doctor before consuming OTC or herbal products, due to the risk of interactions.

Management of cytopenias (use of G-CSF, cycle spacing, and dose titration)

A bone marrow study will be performed on day 22 (± 4 days) of C1 (C1D22) to evaluate the response to treatment by assessing the percentage of blasts and bone marrow cellularity. This is particularly important

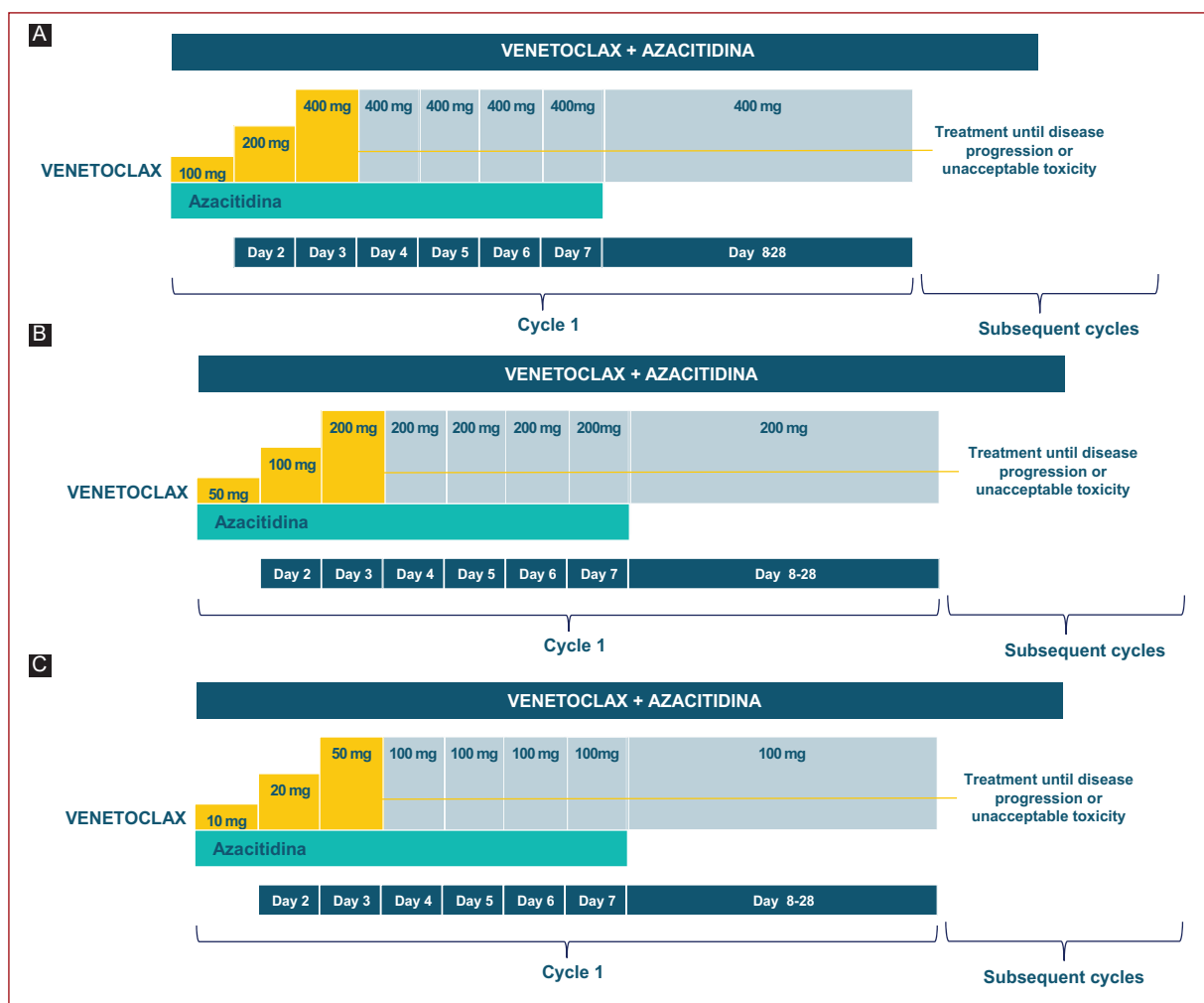


Figure 1. A: venetoclax ramp-up without CYP3A inhibitor. **B:** venetoclax ramp-up with moderate CYP3A inhibitor. **C:** venetoclax ramp-up with potent CYP3A inhibitor*. *Azacitidine must be administered at 75 mg/m² on days 1-7 of each 28-day cycle starting on day 1 of cycle 1.

to guide the timing for starting cycle 2 (C2) of therapy and venetoclax dose titration.

In AML patients, it is common to have grade 3 or 4 neutropenia before starting treatment or during its course, once a response has been achieved. Complete blood counts should be performed throughout the treatment period. The recommendation to interrupt or reduce the dose of drugs in patients with severe neutropenia will differ according to the disease situation. The use of G-CSF is recommended if the patient is in response, as it allows reducing the duration of neutropenia. Several studies^{16,26,27} demonstrate that the use of G-CSF when the patient is in remission does not affect efficacy (response rate and OS) and allows shortening the duration of neutropenia²⁸. On the other hand, suspected infection in a responding patient requires

treatment suspension, immediate initiation of empirical antimicrobial therapy, and the use of G-CSF.

Based on the above, the recommendations for treatment suspension periods due to hematological toxicity, VENAZA dose or day reductions, and the use of G-CSF are as follows:

- C1. In patients with grade 4 cytopenias and no morphological evidence of leukemia in the bone marrow (< 5% blasts, secondary bone marrow aplasia), venetoclax will be discontinued and the complete blood count will be monitored weekly. The start of C2 treatment will be deferred until a neutrophil count of $\geq 0.5 \times 10^9/L$ (ideally $> 1.0 \times 10^9/L$) and platelets $\geq 50 \times 10^9/L$ (ideally $> 100 \times 10^9/L$) is achieved. G-CSF can be used to shorten the days of neutropenia. In case of no peripheral blood recovery after 2 weeks of

medication suspension, a new bone marrow study is recommended to re-evaluate the disease status.

In patients with grade 4 neutropenia where treatment response has not yet been evaluated, or who, after evaluation, do not meet any of the response criteria defined in the ELN recommendations (i.e., CR, CR without peripheral blood recovery [CRi], or marrow leukemia-free state [MLFS]), treatment with venetoclax should be continued until day 28, C2 initiated, and re-evaluated after this. In this case, prophylactic G-CSF administration is not recommended.

– C2 and subsequent:

- Bone marrow study without morphological evidence of leukemia after C1. Once a response is achieved, venetoclax administration in subsequent cycles will be maintained with the same schedule that objective response was achieved (e.g., 28 or 21 days). In subsequent cycles, if cytopenias last longer than one week and the patient remains in remission, it is recommended to reduce the duration of venetoclax by one week (from 28 to 21 days, from 21 to 14 days, from 14 to 7 days) and administer G-CSF for faster recovery. Starting from the 3rd cycle, AZA down titration can also be considered according to the technical specifications if the duration and severity of cytopenias require it²⁴. To 50% if bone marrow cellularity is between 15% and 50%, and to 33% if bone marrow cellularity is < 15%. Another option could be to reduce the duration of AZA days (e.g., to 5 days instead of 7).
- If grade 4 cytopenias persist despite this, the frequency of successive cycles should be prolonged (e.g., every 5 weeks) and/or prophylactic G-CSF added²⁷ (Figs. 2 and 3).
- Bone marrow study with morphological evidence of leukemia. In the event that the blast count in the bone marrow is $\geq 5\%$ after C1, C2 will be initiated on day 29 even if the patient has not shown hematological recovery, since the lack of recovery will be considered due to leukemia. If the blast infiltration does not justify the lack of peripheral blood recovery, venetoclax suspension and delaying the start of the next cycle can be considered individually. As after C1, in patients experiencing persistent/prolonged cytopenias (> 1 week) or new-onset cytopenias while in remission, a bone marrow aspirate should be considered to evaluate the disease situation.

Treatment should be maintained until progression or unacceptable toxicity. It is not recommended to initiate this treatment in regional hospitals without a hematology hospitalization service or a contactable

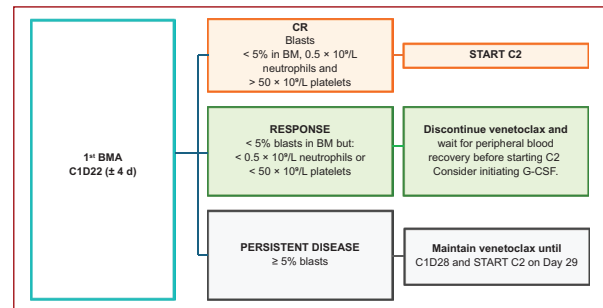


Figure 2. Induction phase. BMA: bone marrow aspirate; G-CSF: granulocyte colony-stimulating factor.

clinical hematologist, especially during the first cycles, when remission has not yet been achieved, and the venetoclax dose has not been adjusted.

Of note, patients ineligible for intensive chemotherapy are not automatically excluded from the possibility of receiving an allogeneic hematopoietic stem cell transplant (allo-HSCT). Some patients may respond favorably to low-intensity treatments, achieving a CR and improving their functional status. In these cases, the indication for allo-HSCT should be evaluated as a potential therapeutic option.

Tumor lysis syndrome prophylaxis

There is a potential risk of TLS in patients treated on venetoclax due to the rapid onset of apoptosis in leukemic cells caused by the inhibition of bcl-2. In AML, certain patients have a higher risk: those with elevated leukocyte counts, elevated lactate dehydrogenase (LDH) levels, presence of circulating blasts, renal insufficiency, increased uric acid, and dehydration²⁹. To reduce the risk of TLS, all patients must receive preventive measures and undergo close analytical monitoring.

It is recommended to have a leukocyte count < 25 $\times 10^9/L$ prior to venetoclax administration. In cases where leukocytes > 25 $\times 10^9/L$ are present, cytorreduction with hydroxyurea (doses up to 75 mg/kg/day PO) or cytarabine (bolus of 100-500 mg/m² IV) will be required prior to initiation. In leukemias with mutations that carry a higher risk of TLS due to increased sensitivity to bcl-2 inhibition (NPM1, IDH1/2 mutations), superior cytorreduction (< 10 $\times 10^9/L$) is recommended prior to venetoclax initiation^{1,30,31}.

All patients must be adequately hydrated (e.g., 2-3 L of glucose-saline solution or 0.9% physiological saline every 24 h) and receive anti-hyperuricemic agents

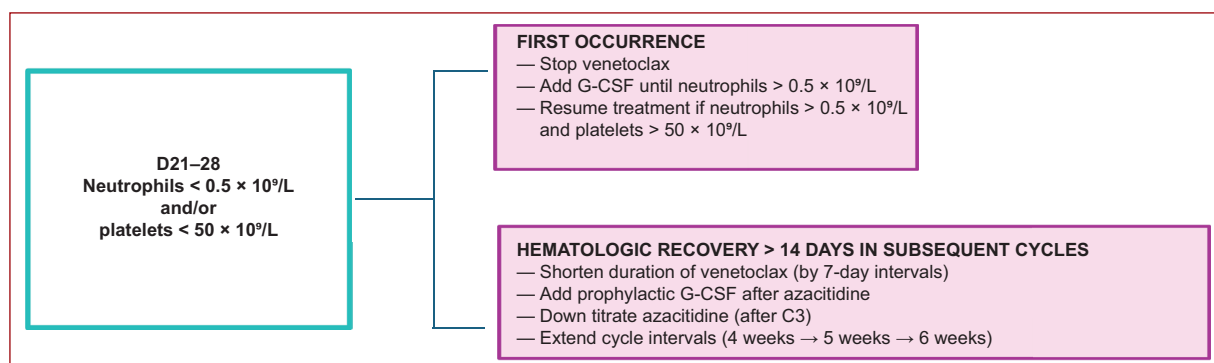


Figure 3. Post-induction phase. G-CSF: granulocyte colony-stimulating factor.

(allopurinol or rasburicase, depending on TLS risk) before C1D1 and during the dose titration phase. In some selected cases where the predictable risk of TLS is frankly low, adequate oral hydration (2-3 L daily) could be considered (Tables 1 and 2).

A blood biochemical analysis (venous balance, potassium, LDH, uric acid, phosphorus, calcium, and creatinine) must be performed and existing anomalies corrected before starting venetoclax treatment. The possibility of TLS should be monitored via blood biochemical analysis at the following points: before the dose, 6 to 8 hours after each new dose escalation, and 24 hours after reaching the final dose.

In the case of patients with risk factors for TLS (e.g., circulating blasts, high burden of leukemia involvement in the bone marrow, elevated LDH levels before treatment, or impaired renal function), additional measures should be considered, including increased monitoring of analytical tests, reduction of the initial venetoclax dose, and even hospitalization.

Anti-infective prophylaxis and dose titration based on concomitant use of moderate/potent CYP3A inhibitors

In the VIALE-A trial¹⁶, 42% of patients presented with neutropenia. The most relevant infectious complications were neutropenic fever (39%) and pneumonia (17%). Furthermore, a meta-analysis of 8 studies on the use of venetoclax in AML or myelodysplastic syndrome showed a rate of febrile neutropenia of 47%³². However, there is no consensus on the type of prophylaxis and its duration.

The latest recommendations from the European Conference on Infections in Leukemia (ECIL) group on

Table 1. TLS risk classification in AML

Low risk	AML with leukocytes < 25 x 10 ⁹ /L and LDH < 2 x ULN
Intermediate risk	AML with leukocytes < 25 x 10 ⁹ /L and LDH ≥ 2 x ULN AML with leukocytes 25-99 x 10 ⁹ /L
High risk	AML with leukocytes > 100 x 10 ⁹ /L

LDH: lactate dehydrogenase; AML: acute myeloid leukemia; ULN: upper limit of normal; TLS: tumor lysis syndrome.

Table 2. Recommended TLS prophylaxis based on TLS risk*

	1 point	2 points
Leukocytes	25-75 x 10 ⁹ /L	> 75 x 10 ⁹ /L
LDH	1-4 x ULN	> 4 x ULN
Uric acid	-	7.5 mg/dL (or > ULN)

*0-1 points: hydration > 2 L/m² PO or IV + allopurinol 300 mg/12-24 h PO ± HC03 1/6M/12 h
2-3 points: hydration > 2 L/m² IV + rasburicase 0.2 mg/kg (single dose 4 h before treatment)
4-6 points: hydration > 2 L/m² IV + rasburicase 0.2 mg/kg for 2-4 days (1st dose 4 h before treatment)
IV: intravenous; LDH: lactate dehydrogenase; AML: acute myeloid leukemia; ULN: upper limit of normal; TLS: tumor lysis syndrome; PO: per os (by mouth).

anti-infective prophylaxis in AML recommend considering the use of prophylaxis regimens similar to those used in patients receiving intensive therapy when using venetoclax in combination with HMA³³. Overall, antifungal prophylaxis is used in patients with severe neutropenia (< 0.5 x10⁹/L) in whom a duration > 7 days is expected. In VIALE-A, only 20% of patients received

antifungal prophylaxis, and the rate of invasive fungal infection was similar regardless of the use of CYP3A inhibitors.

Furthermore, there is also insufficient evidence to establish a recommendation for or vs antibiotic or antiviral prophylaxis, so its use varies according to the recommendations of each center. Unlike azoles, the antiviral and antibiotic agents most widely used in prophylaxis do not require venetoclax dose titration.

Since venetoclax is metabolized mainly by the CYP3A cytochrome, it is important to always assess the need for dose adjustment with any concomitant medication, especially quinolones, macrolides, or azoles. The venetoclax data sheet details most of the interactions²⁵.

In patients requiring concomitant use of venetoclax with potent CYP3A inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, and ritonavir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, fluconazole, isavuconazole, and verapamil), the venetoclax dose must be adjusted (Table 3). It has been reported that the concomitant use of antifungals plus the recommended dose reductions is safe and effective³⁴.

Venetoclax also interacts with P-gp inhibitors, so with these drugs, the venetoclax dose should also be adjusted to 50%. It is highly advisable to review drug interaction guides (<https://cancer-druginteractions.org/checker>) and consult with the pharmacy department of each center to review patient medication.

CETLAM recommendations

Administer antifungal prophylaxis in patients where a neutrophil count $< 0.5 \times 10^9/L$ is expected for > 7 days.

Discontinue prophylaxis in successive cycles when the neutrophil count stabilizes $> 0.5 \times 10^9/L$.

Although the only azole indicated for prophylaxis is posaconazole (potent CYP3A inhibitor), the use of isavuconazole should be considered in some of these patients (moderate inhibitor with a better safety profile, fewer interactions, and QTc interval shortening...).

The venetoclax dose used prior to starting a CYP3A inhibitor should be resumed 2 to 3 days after the inhibitor is discontinued.

Consider antibiotic prophylaxis with neutropenia $< 0.5 \times 10^9/L$, preferably with levofloxacin due to the absence of interactions.

There is no evidence for or vs prophylaxis with acyclovir during treatment. Evaluate its use during the first cycles based on the patient's immunosuppression and following the usual clinical practice of each center.

Table 3. Venetoclax down titration with CYP3A Inhibitors

Potent CYP3A inhibitors	
Posaconazole, itraconazole, ketoconazole, voriconazole, clarithromycin, and ritonavir, among others	Down titrate venetoclax dose to ≤ 100 mg (or by at least 75% if it has already been adjusted for other reasons).
Moderate CYP3A inhibitors	
Isavuconazole, fluconazole, ciprofloxacin, verapamil, diltiazem, and erythromycin, among others.	Down titrate venetoclax by at least 50% (see Fig. 1B).

Toxicities

The most frequently observed adverse events (AEs) with the use of VENZA are hematological, seen in virtually all patients and in most of them with a grade 3 or higher, primarily in the first treatment cycles. By order of frequency, thrombocytopenia, neutropenia, febrile neutropenia, and anemia are observed.

Among the non-hematological AEs, GI issues stand out, such as nausea, constipation, diarrhea, and vomiting. The addition of ondansetron (or another antiemetic) is mandatory in AZA treatment regimens. Skin and subcutaneous tissue reactions at the AZA injection site, hypokalemia, peripheral edema, pyrexia, fatigue, anorexia, infections (most frequently pneumonia), and sepsis can also be observed.

Less frequently, with the administration of each of the drugs, toxicity has been reported in the form of hemorrhages, renal and hepatic toxicity, necrotizing fasciitis, cardiac and pulmonary toxicity, differentiation syndrome, and TLS, among others. For more information, see the AZA and venetoclax data sheets^{24,25}.

Special populations

Elderly patients

It is not necessary to perform a specific dose adjustment for elderly patients. Remember to review polypharmacy in case the patient is receiving any CYP3A or P-gp inhibitors that require modification of the venetoclax dose.

Renal insufficiency

Although venetoclax dose titration is not necessary in patients with renal insufficiency, comprehensive clinical and analytical monitoring is recommended to reduce the risk of TLS, especially in the first cycles. In

patients with severe renal insufficiency, venetoclax should only be administered if the benefit outweighs the risk (no data exists for patients with glomerular filtration values < 30 mL/min, as these patients were excluded from clinical trials). Considering the distribution volume of venetoclax and its high degree of protein binding, it is unlikely that dialysis implies a significant elimination of the drug.

Regarding AZA, if unexplained decreases in serum bicarbonate values occur to < 20 mmol/L, the dose must be down titrated by 50% in the next cycle. If an unexplained increase in serum creatinine or blood uric acid occurs, equal to or greater than twice the baseline values and the upper limit of normal, the next cycle must be delayed until the values return to normal or baseline values, and the dose for the next treatment cycle must be decreased by 50%.

Hepatic insufficiency

Venetoclax dose titration is not recommended in patients with mild or moderate hepatic insufficiency. Patients with moderate hepatic insufficiency should be monitored more closely to detect toxic effects at the start and during the dose adjustment phase. A reduction of at least 50% of the dose is recommended in patients with severe hepatic insufficiency (Child Pugh C).

Regarding AZA, no specific change to the initial dose is recommended in patients with hepatic insufficiency. Dose delay or modification should be individually assessed if an increase ≥ 2 in cytolysis and/or cholestasis enzymes is detected, not explained by other causes after treatment initiation. AZA use is contraindicated in patients with advanced malignant liver tumors.

Recommendation of minimum criteria for the administering center and criteria for inpatient/outpatient treatment regimen

The VENAZA treatment regimen can be administered entirely on an outpatient basis for most patients. According to the physician's criteria, some patients (renal insufficiency, overt leukocytosis, logistics/family support) may need to be hospitalized during the ramp-up, and can be discharged at the end of it if there are no incidents.

Overall, it is recommended to perform the treatment entirely on an outpatient basis provided the center has the following characteristics: a) availability of an onco-hematology day hospital with the possibility of administering adequate hydration during the ramp-up

days; b) an outpatient consultation system (e.g., preferential consultation in a day hospital or similar) that allows visiting patients every 24-48 h during the ramp-up and at least weekly during C1 and in successive cycles according to tolerance; c) a hematology consultation/emergency circuit that allows regulated monitoring of possible AEs during treatment (e.g., blood tests, transfusions, ECG), and d) an on-call hematology service (in-person or reachable) at least during the first cycles.

In case any of these characteristics are not met, the center should evaluate whether to refer the patient to their reference center for acute leukemias for the first treatment cycles or, conversely, admit the patient during the first cycle for serial analytical control and, once the absence of complications is ruled out, continue on an outpatient basis.

It should be considered that cytopenias, in the absence of clinical impact (e.g., fever or congestive heart failure), are not a reason for mandatory admission. It is also recommended that if a circuit for home SC AZA administration is available, it should be used starting from C2 to ensure correct tolerance and absence of adverse reactions in C1.

Response evaluation

To evaluate the efficacy profile early and make dose titrations according to the recommendations of this guide, the following procedure will be followed.

Baseline evaluation (1-14 days prior to treatment initiation)

- Diagnosis: for the biological classification of the disease, the use of the AML diagnostic classification according to the International Consensus Classification (ICC) 2022 and the AML diagnostic classification according to the World Health Organization (WHO) 2022 is advised. Regarding prognostic classification, the proposal by the ELN 2022 does not correctly stratify the risk of this patient group (AML receiving first-line VENAZA therapy), therefore they will be stratified according to the current recommendation of the ELN 2024, based on the mutational status of FLT3-ITD, K/N-RAS, and TP53³⁵.
- Frailty and comorbidities: complete anamnesis with evaluation of patient comorbidities (emphasizing any recent, < 3 months, and/or decompensated medical complications), functional status, and usual medication to determine as objectively as possible the patient's

frailty that will condition non-inclusion in intensive treatment protocols. Serum biochemistry (including venous blood gas analysis, renal function, hepatic function, urates, calcium, phosphate, and LDH), ECG, left ventricular ejection fraction evaluation (isotopic ventriculography [MUGA] or echocardiography), and chest radiography will be required. The use of Ferrara⁸ and HCT-CI⁷ criteria, functional status (ECOG), geriatric assessment scales (G8, VES-13, and GAH), and basal risk of presenting TLS are recommended. To calculate the TLS risk, we will base ourselves on [table 1](#), and cyto-reduction with hydroxyurea (doses up to 75 mg/kg/day PO) or cytarabine (IV bolus of 100-500 mg/m²) will be performed according to the previously established recommendations.

Evaluation in treatment C1

- Ramp-up period (D1-D5): clinical and analytical monitoring every 24 h within the first week of treatment. Clinical follow-up will be performed with toxicity evaluation and analytical assessment to evaluate transfusional support, as well as the appearance of TLS. Blood work: complete blood count and serum biochemistry will be performed, including venous blood gas analysis, hepatic and renal function with specific parameters to detect the appearance of TLS.
- Weeks after ramp-up (D6-D22): clinical and analytical monitoring on a weekly basis, or more frequently if the individualized condition of the patient requires it.
Day 22 of C1 ($\pm$ 4 d): clinical and analytical monitoring with evaluation of the disease at the bone marrow level (bone marrow aspirate performance).

Evaluation in treatment C2

On D1 of treatment, a complete blood count and complete serum biochemistry are recommended, including venous blood gas analysis to determine bicarbonate levels that may require AZA dose adjustment.

During C2, clinical and analytical follow-up is recommended 1-2 times per week according to clinical condition and transfusion requirements.

On day 28 of C2 ($\pm$ 7 d), a bone marrow aspirate will be performed regardless of whether the patient is on venetoclax for 28, 21, or 14 days. This evaluation will be considered the post-induction evaluation if a response had not been achieved after C1, and a first measurable residual disease (MRD) study is recommended.

Evaluation in treatment C3 and subsequent (year 1)

On D1 of treatment, a complete blood count and complete serum biochemistry are recommended.

During C3 and subsequent cycles, clinical and analytical monitoring is recommended individualized to the clinical condition and transfusion requirements.

A bone marrow evaluation will be performed with determination of MRD subsequent to cycles 4, 6, 9, and 12.

Evaluation from treatment year 2

On D1 of treatment, a complete blood count and complete serum biochemistry are recommended.

During C13 and subsequent cycles, clinical and analytical monitoring is recommended individualized to the clinical condition and transfusion requirements.

A bone marrow evaluation will be performed with determination of MRD every 3 months or at the discretion of the investigator according to the evolution of each patient.

The MRD study will be performed by molecular biology in AML patients with the presence of mutation in NPM1, t(8;21), or inv(16). In the rest of AML, MRD will be determined by multiparametric flow cytometry.

Evaluation at relapse or disease progression

Clinical, analytical, and bone marrow control, with a new evaluation of the cytogenetic and molecular profile to assess options with targeted therapy in clinical trials or care if available at the center. Clinical and analytical monitoring at least weekly until a decision is made on whether to opt for bailout therapy. Admission of the patient at any time when the clinical situation requires it at the discretion of each physician. Evaluate the need to contact the palliative support medical team.

Response criteria

It is proposed to evaluate the response according to the recommendations of the ELN 2022³.

Criteria for discontinuing treatment

- Inefficacy:
 - Absence of response after 2 treatment cycles (individualize in each case the toxicities presented by

the patient to administer a maximum of four treatment cycles in the absence of response).

- Maintained partial response after six treatment cycles if there is no clinical benefit or improvement or absence of transfusional requirement.
 - Relapse or progression of the disease at any time.
- Unacceptable toxicity:
- Severe infectious complications requiring persistent hospitalization despite achieving complete response after the 2nd or 3rd treatment cycle.
 - Prolonged severe cytopenias (> 42 days) despite performing the appropriate venetoclax adjustments (down to a minimum of 7 consecutive days) and AZA, the use of G-CSF, and the increase in rest days between cycles in patients who are in response.
 - In any case, in the face of hematological or extra-hematological toxicity > grade 3 (CTCAE v5.0, 2017)³⁶ that persists beyond 42 days of treatment despite the appropriate dose titration of both drugs and the use of usual supportive measures (consider risk/benefit on an individualized basis).

Discussion

The introduction of combined VENAZA treatment in AML patients ineligible for intensive chemotherapy represents a significant change in the prognosis of this disease. Compared to AZA, the VENAZA combination has been shown to considerably improve response rates and OS. These results consolidate VENAZA as the new standard for this population, with evident clinical benefit.

However, the management of patients on VENAZA treatment requires significant adaptations regarding their follow-up, timing of response evaluation, use of G-CSF, antifungal prophylaxis, TLS prophylaxis, and dose adjustments to avoid toxicities. These specificities require a standardized and specialized approach that guarantees safe and effective implementation. Therefore, this management guide is essential to standardize practice and optimize the use of VENAZA in real life. Furthermore, it allows for the prospective evaluation of its efficacy and safety in clinical practice, thus contributing to improving the outcomes and quality of life of these patients.

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None.

Conflicts of interest

None.

Ethical considerations

Protection of persons and animals. The authors declare that the procedures followed conformed to the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Ethics Committee of the institution.

Confidentiality, informed consent, and ethical approval. The study does not involve personal patient data nor does it require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for the writing of this manuscript.

References

1. Solans M, Sanvisens A, Ameijide A, Merino S, Rojas D, Alemán A, et al. Incidence of myeloid neoplasms in Spain (2002-2013): a population-based study of the Spanish network of cancer registries. *Sci Rep.* 2022;12:323.
2. Talati C, Dhulipala VC, Extermann MT, Al Ali N, Kim J, Komrokji R, et al. Comparisons of commonly used front-line regimens on survival outcomes in patients aged 70 years and older with acute myeloid leukemia. *Haematologica.* 2020;105:398-406.
3. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an International expert panel on behalf of the ELN. *Blood.* 2022;140:1345-77.
4. Löwenberg B, Ossenkoppele GJ, van Putten W, Schouten HC, Graux C, Ferrant A, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med.* 2009;361:1235-48.
5. Ossenkoppele G, Löwenberg B. How I treat the older patient with acute myeloid leukemia. *Blood.* 2015;125:767-74.
6. Gener G, Morgades M, Garrido A, et al. Supervivencia global en pacientes ≥70 años con leucemia aguda mieloblástica de pronóstico favorable tratados con dos estrategias diferentes. Experiencia del grupo CETLAM. LXII Congreso Nacional de la SEHH y XXXVI Congreso Nacional de la SETH, Virtual 26-30 Octubre 2020. PO-124. Disponible en: <https://www.sehh.es/images/stories/recursos/2020/11/20/congreso/HAEMATOLOGICA-comunicaciones-SEHH.pdf>
7. Giles FJ, Borthakur G, Ravandi F, Faderl S, Verstovsek S, Thomas D, et al. The haematopoietic cell transplantation comorbidity index score is predictive of early death and survival in patients over 60 years of age receiving induction therapy for acute myeloid leukaemia. *Br J Haematol.* 2007;136:624-7.
8. Ferrara F, Barosi G, Venditti A, Angelucci E, Gobbi M, Pane F, et al. Consensus-based definition of unfit to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. *Leukemia.* 2013;27:997-9.
9. Gupta V, Chun K, Yi QL, Minden M, Schuh A, Wells R, et al. Disease biology rather than age is the most important determinant of survival of patients > or = 60 years with acute myeloid leukemia treated with uniform intensive therapy. *Cancer.* 2005;103:2082-90.
10. Kantarjian H, O'Brien S, Cortés J, Giles F, Faderl S, Jabbour E, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognosis models for outcome. *Cancer.* 2006;106:1090-8.
11. Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol.* 2012;21:2670-7.

12. Fenaux P, Mufti GJ, Hellström-Lindberg E, Santini V, Gattermann N, Germing U, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol*. 2010;28:562-9.
13. Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with > 30% blasts. *Blood*. 2015;126:291-9.
14. Vives S, Martínez-Cuadrón D, Bergua, Algarra L, Tormo M, Martínez-Sánchez MP, et al. A phase 3 trial of azacitidine versus a semi-intensive fludarabine and cytarabine schedule in older patients with untreated acute myeloid leukemia. *Cancer*. 2021;127:2003-14.
15. Wei AH, Montesinos P, Ivanov V, DiNardo CD, Novak J, Laribi K, et al. Venetoclax plus LDAC for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020;135:2137.
16. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and Venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383:617-29.
17. Informe de posicionamiento terapéutico. PT 119-2023/V1/21032023 [Internet]. Agencia Española de Medicamentos y Productos Sanitarios, REValMed SNS; 21/03/2023. Disponible en: <https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/2023/IPT-119-2023-Venclyxto-venetoclax.pdf>
18. Balducci L, Extermann M. Management of cancer in the older person: a practical approach. *Oncologist*. 2000;5:224-37.
19. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen MLG, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol*. 2014;32:2595-603.
20. Decoster L, van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†. *Ann Oncol*. 2015;26:288-300.
21. Saliba D, Elliott M, Rubenstein LZ, Solomon DH, Young RT, Kamberg CJ, et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. *J Am Geriatr Soc*. 2001;49:1691-9.
22. Soubeyran P, Bellera C, Goyard J, Heitz D, Curé H, Rousselot H, et al. Screening for vulnerability in older cancer patients: the ON-CODAGE Prospective Multicenter Cohort Study. *PLoS One*. 2014;9:e115060.
23. Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G - 8 geriatrics screening tool. *Ann Oncol*. 2012;23:2166-72.
24. Azatidina Sandoz. Ficha técnica [Internet]. Centro de información online de medicamentos de la Agencia Española de Medicamentos y Productos Sanitarios; enero 2024. Disponible en: https://cima.aemps.es/cima/pdfs/es/ft/85133/85133_ft.pdf
25. Venclyxto. Dispob. Ficha técnica [Internet]. Centro de información online de medicamentos de la Agencia Española de Medicamentos y Productos Sanitarios; agosto 2023. Disponible en: https://cima.aemps.es/cima/docht/ml/ft/161138002/FT_161138002.html
26. Liu B, Gou Y, Qiao Y, Qiao Y, Jian J. The efficacy and adverse events of venetoclax in combination with hypomethylating agents treatment for patients with acute myeloid leukemia and myelodysplastic syndrome: a systematic review and meta-analysis. *Hematology*. 2020;25:414-23.
27. Maschmeyer G, Bullinger L, Gardia-Vidal C, Herbrecht R, Maertens J, Menna P, et al. Infectious complications of targeted drugs and biotherapies in acute leukemia. Clinical practice guidelines by the European Conference on Infections in Leukemia (ECIL), a joint venture of the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the International Immunocompromised Host Society (IHS) and the European Leukemia Net (ELN). *Leukemia*. 2022;36:1215-26.
28. Jonas BA, DiNardo C, Fracchiolla N, Pristupa A, Ishizawa K, Jin J, et al. Use of CYP3A4 and impact on outcomes in patients with acute myeloid leukemia treated with venetoclax plus azacitidine in the VIALE-A study. *Am J Hematol*. 2022;97:E422-25.
29. Jonas BA, Pollyea DA. How we use venetoclax with hypomethylating agents for the treatment of newly diagnosed patients with acute myeloid leukemia. *Leukemia*. 2019;33(12):2795-804.
30. DiNardo CD, Pratz K, Panayiotidis P, Wei X, Vorobyev V, Illés A, et al. The impact of post-remission granulocyte colony-stimulating factor use in the phase 3 studies of venetoclax combination treatments in patients with newly diagnosed acute myeloid leukemia. *HemaSphere*. 2022;6:409-10.
31. Pratz KW, DiNardo CD, Selleslag D, Li J, Yamamoto K, Konopleva M, et al. Postremission cytopenia management in patients with acute myeloid leukemia treated with venetoclax and azacitidine in VIALE-A. *Am J Hematol*. 2022;97:E416-E419.
32. Montesinos P, Loreno I, Martín G, Sanz J, Pérez-Sirvent ML, Martínez D, et al. Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model. *Hematologica*. 2008;93:67-74.
33. DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, et al. Venetoclax combined with decitabine or azacitidine in treatment-naïve, elderly patients with acute myeloid leukemia. *Blood*. 2019;133:7-17.
34. Richard-Carpentier G, DiNardo CD. Venetoclax for the treatment of newly diagnosed acute myeloid leukemia in patients who are ineligible for intensive chemotherapy. *Ther Adv Hematol*. 2019; 10:2040620719882822.
35. Döhner H, DiNardo CD, Appelbaum RA, Craddock C, Dombret H, Ebert BL, et al. Genetic Risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations. *Blood*. 2024;144:2169-73.
36. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [Internet]. U.S. Department of Health and Human Services; 27 nov 2017. Disponible en: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf