How do I manage the myelotoxicity of venetoclax and azacitidine in patients with newly diagnosed acute myeloid leukemia?

Aleksander Salomon-Perzyński, Bożena Katarzyna Budziszewska

Department of Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland

Address for correspondence:
Bożena Katarzyna Budziszewska
Department of Hematology
Institute of Hematology
and Transfusion Medicine
Indiry Gandhi 14
02–776 Warsaw, Poland
e-mail: bbudziszewska@ihit.waw.pl

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ABSTRACT

The introduction of venetoclax in combination with azacitidine (venAZA) represents a turning point in the treatment of patients with newly diagnosed acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy due to age, performance status and/or significant comorbidities. Conducting venAZA treatment in routine clinical practice, however, can present significant difficulties, due to both the substantial myelotoxicity (severe hematological side effects during venAZA are experienced by the majority of patients) and the clinical characteristics of AML patients not eligible for intensive chemotherapy. Thus, for optimal treatment outcomes, appropriate patient qualification for treatment and robust management of venAZA hematological toxicity are crucial. Retrospective data indicate that modification of venetoclax and azacitidine dosing during treatment is associated with longer treatment duration and translates favourably into longer overall survival. Here, the authors outline the management of patients with newly diagnosed AML in whom treatment with venAZA is complicated by profound myelosuppression.

Key words: acute myeloid leukemia, elderly, drug toxicity, venetoclax, azacitidine, neutropenia, thrombocytopenia

INTRODUCTION

The introduction of venetoclax in combination with azacitidine (venAZA) represents a turning point in the treatment of patients with newly diagnosed acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy due to age, performance status and/or significant comorbidity burden. This group of patients represents a particularly challenging population in daily clinical practice. Firstly, elderly patients are more likely to be burdened with high-risk cytogenetic and/or molecular aberrations according to the European LeukemiaNet (ELN) [1]. Secondly, advanced age, poorer performance status, as well as multimorbidity, result in an increased risk of treatment-related severe adverse events. Until recently, therapeutic options in patients ineligible for intensive chemotherapy were limited to hypomethylating agents (HMA) given as monotherapy (AZA or decitabine [DEC]) [2, 3] or non-intensive chemotherapy protocols, i.e. cladribine combined with low-dose cytarabine (Ld-AC) (the Polish Adult Leukemia Treatment Group [PALG] treatment protocol for elderly AML patients) [4], cladribine combined with Ld-AC administered alternately with DEC (MD Anderson Cancer Centre [MDACC] treatment protocol) [5] or Ld-AC in monotherapy [2, 3]. In general, these therapeutic strategies were characterized by limited efficacy, especially in terms of long-term disease control, with combined rates of complete remission (CR) and complete remission with incomplete hematopoietic recovery (CRi) (CR + CRi) and median overall survival (OS) of 28% and 10.4 months (for AZA in monotherapy [3]), 26% and 7.7 months (for DEC in monotherapy [2]), 37% and 6.9 months (for PALG protocol [4]) and 68% and 13.8 months (for MDACC protocol [5]), respectively. The randomized phase 3 VIALE-A trial showed significant superiority of venAZA treatment over AZA + placebo in terms of both CR + CRi (66.4% in the venAZA arm vs. 28.3% in the control arm) and OS (median, 14.7 months vs. 9.6 months, respectively, in the venAZA and AZA + placebo arms; updated November 2022) in a group of 431 patients with newly diagnosed AML who, due to age (≥ 75 years) or performance status (2–3 acc.

to the Eastern Cooperative Oncology Group [ECOG] scale) or significant comorbidities, were ineligible for intensive chemotherapy [6, 7]. While the clinical efficacy of venAZA is undeniable, its toxicity is unremarkable. In the VIALE-A trial, serious adverse events (SAE) were experienced by 85% of patients treated with venAZA (and 77% of patients treated in the control arm). Serious AEs (at least grade 3 acc. to the Common Terminology Criteria for Adverse Events [CTCAE]) were predominantly hematological toxicity, including thrombocytopenia (platelet count [PLT] < 50 G/L) (46% in the venAZA arm vs. 40% in the control arm) and neutropenia (absolute neutrophil count [ANC] < 1.0 G/L) (43% in the venAZA arm vs. 29% in the control arm) and, in particular, neutropenic fever (43% in the venAZA arm vs. 19% in the control arm) [7].

Translating the results of a clinical trial into success in routine clinical practice requires appropriate management of treatment-related adverse events. This is particularly relevant for treatment with venAZA, during which, severe hematological AEs are experienced by 82% of treated patients [6], which can significantly complicate the safe management of therapy in the outpatient setting. Here, the authors outline the principles for the management of patients with newly diagnosed AML in whom treatment with venAZA is complicated by profound myelosuppression.

CLINICAL CASE (PART I)

A 68-year-old female patient with a history of serous ovarian cancer after surgery and adjuvant chemotherapy (paclitaxel + carboplatin) and a history of viral hepatitis (type A and type B) was diagnosed with AML with a normal karyotype, NPM1 gene mutation and coexisting internal tandem duplication (ITD) of the *FLT3* gene. Initially, the patient was in severe general condition with an ECOG performance status of 4 due to respiratory failure in the course of pneumonia with bilateral pleuritis and urinary retention in the course of nephrolithiasis. Cytoreductive treatment with hydroxycarbamide, intensive supportive treatment, and physical and pulmonary rehabilitation were provided. Once significant improvement in the patient's general condition was achieved, venAZA treatment was initiated. During therapy, primary prophylaxis of invasive fungal infection (posaconazole), prophylaxis of hepatitis B virus reactivation(tenofovir) and transient antibacterial prophylaxis (levofloxacin) were applied. During the first venAZA cycle, the patient's condition gradually improved until she returned to full-life activity. Rapid platelet regeneration was observed; importantly, the patient was initially diagnosed with CTCAE grade 4 thrombocytopenia and was resistant to platelet transfusions (the patient was identified with anti-human leukocyte antigen [HLA] class I antibodies). On day 28 of the first venAZA cycle, a hematological evaluation was performed finding only 1.4% myeloblasts in the bone marrow aspirate. Hemoglobin was 9 g/dL, PLT 220 G/L but grade 4 neutropenia was observed (ANC 0.3 G/L). Hence, CRi was achieved. It was decided to postpone the second cycle venAZA until recovery of ANC, but no longer than 14 days.

DISCUSSION (PART I)

The exclusion that the observed cytopenias are secondary to the underlying disease (i.e. due to 'crowding out') is essential for venAZA dosing modification. In the VIALE-A study, in the vast majority of venAZA-treated patients who achieved at least CR with partial haematopoietic recovery (CRh), so-called blast clearance, defined as a reduction in the percentage of blasts in the bone marrow < 5%, was achieved at the end of cycle 1 of treatment (76% of patients); a further 11%, 4% and 5% of patients achieved blast clearance at the end of cycle 2, 3 and 4 of venAZA, respectively [8]. Hence, in order to determine the origin of the observed cytopenias, an early hematological evaluation is mandatory, i.e. performed at week 4 (day 21–28) of the 1st venAZA cycle [9] (It should be noted that according to the ELN 2022 recommendation [10] it is acceptable to perform the hematological evaluation even earlier, i.e. between days 14 and 21 of the 1st venAZA cycle). In patients who have not achieved blast clearance, it is recommended to start another cycle of treatment, regardless of the depth and duration of cytopenias [6, 9]. In contrast, the initiation of the next venAZA cycle in patients with blast clearance should be delayed until at least partial haematopoietic regeneration has been achieved (i.e. when ANC > 0.5 G/L and PLT > 50 G/L); the interruption in venetoclax dosing should not last longer than 14 days [6, 8–10]. It is important to stress that in some modifications of the venAZA protocol, more restrictive morphological criteria have been applied that must be met in order to start the next venAZA cycle in patients who have achieved blast clearance (e.g. ANC > 1.0 G/L and PLT > 50 G/L according to the protocol modification provided by BC Cancer experts [protocol available online: http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Leukemia-BMT/ULKAMLAVEN_Protocol.pdf] or ANC > 1.0 G/L and PLT > 75 G/L according to the protocol modification provided by National Health Service experts [protocol available online: https://nssg.oxford-haematology.org.uk/myeloid/protocols/ML-84-azacitidine-and-venetoclax-covid-19.pdf]). In patients who have achieved blast clearance but have not achieved the ANC and PLT values required to start another venAZA cycle, if ANC is still < 0.5 G/L after a 7-day treatment-free interval, it is reasonable to use granulocyte colony-stimulating factor (G-CSF) to hasten recovery [10].

Neutropenic fever and infections are the most significant clinical complications of venAZA therapy. In the VIALE-A study, 43% of patients treated in the investigational arm developed neutropenic fever [6, 7]. Retrospective data indicate that one in three AML patients treated with venetoclax combined with HMA develops at least one infection of confirmed bacterial etiology, and one in two patients

requires at least one hospitalization for neutropenic fever during antileukemic therapy [11]. In the light of real-world evidence, particular vigilance regarding infectious complications should be exercised in patients starting venetoclax and HMA combinations, since one in three patients will suffer at least one episode of neutropenic fever during the first cycle of therapy [12].

Should antifungal prophylaxis be used in patients treated with venAZA?

The rationale for antifungal prophylaxis during venAZA remains an open question. Retrospective data indicate a rather low incidence of invasive fungal infection (IFI) in patients treated with venAZA. Cases of "proven" and "probable" IFI affect approximately 5% of patients [11, 13]. In contrast, reports that also include 'possible' cases indicate that IFI complicates the course of treatment in 13–17% of patients [13, 14]. However, these data should be interpreted with caution, as the prevalence of IFI in AML patients may be influenced by many factors beyond therapy, including, the geographical location of the site, local climatic and epidemiological conditions and the non-specific methods used in the site to prevent infectious complications, as well as local antibiotic policy, including neutropenic fever treatment guidelines. Considering this, it should be emphasized that there are also reports indicating a significantly higher incidence of IFI in AML patients treated with venAZA (in one retrospective analysis of 61 AML patients treated with AZA or venAZA, the overall proportion of 'proven' and 'probable' IFI cases was 19.6% [15]). Regardless of the variation in reported IFI rates, it is noteworthy that IFI most often complicates the early phase of venAZA therapy (in one published study, the highest risk of IFI was in the first 10 days of the first venAZA cycle [13]. In a recent position paper on the use of antifungal prophylaxis in adult AML patients treated with novel therapies, experts from the European Hematology Association made a conditional recommendation in favour of providing antifungal prophylaxis in AML patients treated with venetoclax (with a preference towards the use of an azole antifungal agents) [16]. In this context, it is worth noting that the protocol of the VIALE-A clinical trial [6] required antimicrobial, antiviral and antifungal prophylaxis in all patients with CTCAE grade 4 neutropenia but the drugs used in the prophylaxis were selected by the investigator based on local guidelines and epidemiological situation of the site.

Due to drug interactions between venetoclax and azoles, a dose reduction of venetoclax is mandatory for the concomitant use of venetoclax and azole, both in the titration phase and in the fixed-dose phase [17]. However, there is a question of whether the concomitant use of venetoclax and azole increases the myelosuppressive effect of venetoclax despite a reduction in the venetoclax dose. Rausch et al. retrospectively assessed the time to peripheral blood count recovery in terms of neutrophils (ANC > 1.0 G/L) and platelets (PLT > 100 G/L) during the first treatment cycle in a group of 64 AML patients receiving first-line venetoclax in combination with HMA of whom 73% received azole antifungal prophylaxis (posaconazole, 27%; voriconazole, 14%; isavuconazole 31%; fluconazole, 2%). There were no significant differences in median time to ANC recovery between azole-treated and non-azole-treated patients (median, 37 and 39 days, respectively); however, the statistically significantly (but not clinically) longer median time to PLT recovery was observed in azole-treated patients (median, 28 and 22 days, respectively) [18].

A CLINICAL CASE (PART II)

The second venAZA cycle was started after a 14-day break when full recovery of peripheral blood count (PLT 220 G/ /L, ANC 1.5 G/L) was achieved. During the 2nd cycle, two episodes of uncomplicated grade 4 neutropenia according to CTCAE were observed, each lasting longer than 7 days. Venetoclax dosing was discontinued and resumed after ANC increase > 1.0 G/L. G-CSF was used to reduce the duration of severe neutropenia. Cycle two was completed without further complications, the venetoclax dosing duration was reduced to 21 days in subsequent 28-day venAZA cycles.

DISCUSSION (PART II)

Uncomplicated grade 4 neutropenia (ANC < 0.5 G/L) or thrombocytopenia (PLT < 25 G/L) occurring during the administration of venAZA cycle in patients with blast clearance and persisting for at least 7 days (hereafter referred to as 'significant cytopenia') requires the withholding of venetoclax dosing [17]. After the first episode of significant cytopenia, following an increase in ANC > 1.0 G/ /L and blood PLT > 50 G/L, venetoclax is resumed with unchanged dosing (i.e., 28 days of venetoclax in 28-day venAZA treatment cycles) [17]. With a subsequent episode of significant cytopenia, venetoclax dosing is stopped during the cycle, then (after an increase in ANC > 1.0 G/L or PLT > 50 G/L) venetoclax is resumed at an unchanged dose, but its dosing duration is reduced to 21 days [17]. If significant cytopenias continue to complicate the course of treatment despite a reduction in venetoclax dosing to 21 days, a further shortening of venetoclax dosing to 14 [9, 10] (after the third episode of significant cytopenias) or even 7 days (after the fourth episode of significant cytopenias) in 28-day treatment cycles may be considered [10, 19]. It should be emphasised that in the VIALE-A trial, the venetoclax dosing duration was not shortened to < 21 days. Patients who had their venetoclax dosing time shortened to 21 days and still did not show signs of recovery, defined as an increase in ANC and PLT of at least 25% relative to the nadir in the subsequent 21 days after the end of the cycle, were recommended to have their AZA dose reduced

by 33% and 50% with bone marrow cellularity < 15% and 15–50%, respectively [6]. Overall, 36% of patients treated in the venAZA arm required AZA dose reduction with a median of 5 cycles from blast clearance to the first AZA dose reduction [8].

Should we be concerned about the negative impact of shortening venetoclax dosing on venAZA treatment outcomes?

Treatment with venAZA should be considered particularly through its toxicity. This is because it is administered to the subpopulation of AML patients that is particularly susceptible to treatment-related complications. A recently published retrospective study, which included 169 patients with newly diagnosed AML with a median age of 77 years, shows that modifications to the venetoclax dosing regimen (interruptions in venetoclax dosing during a cycle, shortening of venetoclax dosing time, postponement of the next cycle) from at least the second cycle of venetoclax treatment in combination with HMA is required in 60% of patients. Notably, these modifications are associated with a longer overall duration of venAZA treatment, which translates into prolonged OS [20]. In another retrospective study that included 13 patients with newly diagnosed AML with a median age of 79 years, eight of whom had high-risk disease according to the ELN, a reduction in venetoclax dosing to 14 days (compared to venetoclax administered for 28 days) starting with the first venAZA cycle was associated with a more favourable safety profile, a shorter hospital stay, and, most importantly, had no negative impact on treatment outcomes, both in terms of CR + CRi (75%) and OS (median OS not achieved during the median follow-up period of 5 months) [21]. At the last American Society of Hematology conference, another retrospective analysis was presented including 82 patients with previously untreated AML (70% were patients with the high-risk disease according to the ELN criteria) in whom venetoclax dosing was reduced to 7 days starting with the 1st venAZA cycle (7/28 regimen) [19]. The median time to recovery of peripheral blood counts in terms of neutrophils (ANC > 1.0 G/L) and platelets (PLT > 100 G/L) was 36 and 31 days, respectively. The overall percentage of CR + CRi was 68% (compared to 66.4% in the VIALE-A study in the venAZA arm), with completely different kinetics of blast clearance (42% and 54% CR + CRi were achieved, respectively, after 1 and 2 cycles of venAZA 7/28) than in the cited VIALE-A study (in patients who achieved at least CRh, blast clearance was observed in 76%, 11%, 4% and 5% of cases, after 1, 2, 3 and 4 cycles of venAZA 28/28, respectively). At a median follow-up of 5 months, the median OS was 13 months. 61% of patients who achieved CR or CRi required venetoclax dosage modification (reduction of venetoclax duration from 7 to 5 days, reduction of venetoclax daily dose from 400 to 200 mg or extension of cycle intervals from 4 to 5 weeks), mainly due to hematological toxicity [19]. Taken together, these data suggest that shortening venetoclax dosing does not harm treatment outcomes, but does not completely prevent hematological complications. This requires confirmation in randomized prospective studies.

Should we be concerned about the use of G-CSF in patients in CR/CRi during venAZA?

The use of G-CSF in the adjuvant treatment of AML remains controversial. However, a recently published large retrospective analysis presented by Kang et al. [22], which included 315 patients treated with intensive chemotherapy (3 + 7 regimen), showed no negative effect of G-CSF used pre-emptively (treatment with G-CSF started when the neutrophil count was < 1.0 G/L) or therapeutically (treatment with G-CSF started when neutropenic fever occurred) on AML relapse-free survival and OS. In a 2022 abstract, DiNardo et al. [23] summarized the impact of G-CSF use on the outcome of patients with AML who achieved CR or CRi during venAZA treatment. One in 2 patients with CR/CRi during venAZA received G-CSF (median time from blast clearance to first G-CSF administration was 36 days; range, 2–483 days). The use of G-CSF in this group did not harm either duration of response or OS [23].

CLINICAL CASE (PART III)

On the day of starting the third cycle of venAZA, the patient developed a bacterial infection of an unknown origin. Severe neutropenia was not observed at that time. Broad-spectrum antibiotic therapy was administered, achieving a rapid clinical response. The third cycle of venAZA was again complicated by significant neutropenia. Venetoclax was again withheld and G-CSF was administered. After ANC regeneration, venetoclax was resumed. The duration of venetoclax was reduced to 14 days in subsequent treatment cycles.

SUMMARY

Managing venAZA in routine clinical practice can present difficulties due to both the toxicity of the treatment itself and the clinical characteristics of AML patients not eligible for intensive chemotherapy. Hence, to achieve optimal treatment outcomes, the key issues are: 1) appropriate qualification of the patient for venAZA, taking into account not only the medical indications and contraindications but also the patient's socioeconomic conditions, the distance between the patient's place of residence, the ematology centre and the nearest hospital capable of treating severe therapy-related adverse events, the availability of the patient's general practitioner and the possibility of cooperation between him/her and the treating hematologist; 2) robust management of myelosuppression during venAZA. The implementation of the second condition requires a hematological assessment between days 21 and 28 of

the first venAZA cycle and an appropriate modification of venetoclax and azacitidine dosing in the next cycles. To this end, it is important that each treating hematology centre develops clear rules for modifying the venAZA regimen drug dosing, taking into account local patient care capacity.

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