VIA MEDICA

REVIEW ARTICLE

Hematology in Clinical Practice
2022, vol. 13, no. 3–4, 112–122
DOI: 10.5603/HCP.a2022.0018

ISSN: 2720–1015
e-ISSN: 2720–2690

Practical aspects of the use of ventoclax in combination with azacitidine for the treatment of newly diagnosed acute myeloid leukaemia in patients ineligible for intensive chemotherapy

Andrzej Szczepaniak[1], Lidia Gil[1], Sebastian Giebel[2], Grzegorz Helbig[3], Tomasz Wróbel[4], Jan Maciej Zaucha[5], Bożena Budziszewska[6], Agnieszka Wierzbowska[7]

[1]Department and Clinic of Haematology and Bone Marrow Transplantation, Medical University of Karol Marcinkowski in Poznań, Poland
[2]Department of Bone Marrow Transplantation and Onco-Haematology, National Oncology Institute of Maria Skłodowska-Curie — National Research Institute, Branch in Gliwice, Poland
[3]Department of Haematology and Bone Marrow Transplantation, Medical University of Silesia in Katowice, Poland
[4]Department of Haematology, Blood Neoplasms and Bone Marrow Transplantation, Wroclaw Medical University, Poland
[5]Department and Clinic of Haematology and Transplantology, Medical University of Gdańsk, Poland
[6]Department of Haematology and Transfusion Medicine, Institute of Haematology and Transfusiology in Warsaw, Poland
[7]Department and Clinic of Haematology, Medical University of Lodz, Poland

Abstract

The aim of treating elderly patients with acute myeloid leukaemia (AML) ineligible for intensive chemotherapy is to extend survival, but treatment results are often unsatisfactory. Therapy with venetoclax combined with azacitidine allowed remission in two-thirds of patients and significantly prolong the median overall survival. The treatment is increasingly used in clinical practice and establishes a new medical standard. The use of venetoclax in treating AML requires knowledge of drug use rules and their individualization. This review summarizes critical elements of the clinical practice of venetoclax use in combination with azacitidine regarding the dosing regimen, management of cytopenias during therapy and treatment adjustments to prevent drug-to-drug interactions. Treatment with venetoclax can cause the risk of tumor lysis syndrome (TLS), and therefore step-wise dose ramp-up is required with the prophylaxis of TLS and reduction in leucocyte count. Cytopenias that occur during the therapy affect most of the patients; nevertheless, it is not recommended to modify the treatment until the remission of the disease. In haematologic toxicity after disease remission, it is recommended to delay the next cycle and shorten the treatment while maintaining the dose. Knowledge about venetoclax drug-to-drug interactions is necessary for an efficacious and safe therapy. It is essential to reconsider the rationale behind using some agents, e.g., azole derivatives commonly used in the prophylaxis of invasive fungal infections, as well as to be aware of the rules of venetoclax dosing. Detailed knowledge of the above aspects of therapy is essential to ensure the continuity, safety, and efficacy of venetoclax with azacitidine.

Key words: acute myeloid leukaemia, azacitidine, cytopenia, CYP3A, tumour lysis syndrome, venetoclax

Hematology in Clinical Practice 2022; 13, 3–4: 112–122

Address for correspondence: Andrzej Szczepaniak, Katedra i Klinika Hematologii i Transplantacji Szpiku, Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu, ul. Szamarzewskiego 84, 60–569 Poznań, Poland, phone +48 61 854 93 83, fax +48 61 854 93 56, e-mail: ajjszczepaniak@gmail.com

Introduction

Acute myeloid leukaemia (AML) is the most common type of acute leukaemia in adults [1, 2] AML is characterized by the production of immature cells (named blasts) deriving from malignantly transformed myeloid cells, which proliferate and accumulate in the bone marrow. The end of the last decade was a period of intensive development of AML therapies, both those intended for patients eligible for intensive therapy, as well as breakthrough therapies for the treatment of elderly patients, the most difficult group of patients who often did not qualify for intensive treatment. These patients have previously been treated with low-dose cytarabine (LDAC) and hypomethylating drugs (HMA) — azacitidine (AZA) or decitabine. As older AML patients are more likely to have unfavourable risk factors such as complex karyotype and *TP53* gene mutations [3], the response to reduced-intensity treatment has been unsatisfactory. These non-intensive therapies provided short-term disease control with an acceptable quality of life, but the prognosis was poor with an expected overall survival (OS) ≤ 12 months [4–6]. Numerous clinical trials have evaluated the effectiveness of various combination therapies based on LDAC or HMA in the elderly patients with AML. Gemtuzumab ozogamicin with LDAC [7], lintuzumab with LDAC [8], durvalumab with AZA [9], avelumab with AZA [10], and entospletinib with decitabine [11] showed no benefit in terms of survival in this difficult-to-treat group of patients. The introduction of venetoclax to the therapy of patients with newly diagnosed AML was a breakthrough. Venetoclax in combination with a hypomethylating drug in elderly people ineligible for intensive treatment allows for a high remission rate and prolongation of survival [12, 13] with maintaining the health-related quality of life (HRQoL) [14].

Venetoclax is a potent, selective inhibitor of the anti-apoptotic protein BCL-2. Overexpression of the BCL-2 protein often observed in the myeloid and lymphoid neoplasms, is responsible for reduced apoptosis of malignant cells and resistance to chemotherapy. Overexpression of the BCL-2 protein also contributes to the chemoresistance of chronic lymphocytic leukaemia (CLL) and AML blasts and is associated with poorer treatment outcomes [15]. The mechanism of action of venetoclax, consisting of inhibition of BCL-2 protein activity and induction of apoptosis of leukemic cells, led to the initiation of clinical trials in AML. Venetoclax monotherapy showed moderate efficacy in the treatment of relapsed and refractory AML with an acceptable toxicity profile [16]. As the preclinical studies demonstrated the synergy between venetoclax and hypomethylating drugs and cytarabine [17, 18], early-phase clinical trials were initiated [13, 19]. Based on their results the combination therapies based on venetoclax were registered in the United States for the treatment of newly diagnosed AML in patients ineligible for intensive chemotherapy [20]. The results of the prospective, randomized phase III study, VIALE-A, confirmed the superiority of venetoclax in combination with azacitidine over azacitidine + placebo in terms of remission rate and overall survival in patients ineligible for intensive induction therapy [12]. The results of the VIALE-A study led to the creation of a new standard of treatment in the group of patients with AML and the registration of venetoclax in Europe [21]. This article summarizes the current knowledge on the use of the combination of venetoclax with AZA and discusses the practical aspects of this therapy.

Venetoclax in combination with azacitidine

Proteins from the BCL-2 (B-cell lymphoma 2) family play an important role in the mitochondrial regulation of apoptosis [22]. AML cells are characterized by high expression of BCL-2 proteins, the level of which is a factor determining the response to chemotherapy [23]. In preclinical studies venetoclax, a selective BCL-2 inhibitor, induced apoptosis in tumour cells dependent on these proteins for survival. However, in AML monotherapy, the drug showed limited efficacy [16]. This contributed to the search for drug combinations based on venetoclax. DNA hypomethylation of abnormally methylated genes involved in cell cycle regulation, differentiation and cell death pathways may lead to their re-expression and sensitization of AML cells to the proapoptotic effects of venetoclax [24, 25]. Based on these premises, a phase Ib clinical trial was conducted to evaluate the safety and efficacy of venetoclax in combination with HMA in previously untreated patients ≥ 65 years of age not eligible for intensive chemotherapy. The study involved 145 patients, almost half of whom had unfavourable cytogenetic risk factors, and every fourth patient had secondary AML. The median age (range) was 74 years (65–86 years). For the expansion phase of the study, i.e. the inclusion of additional patients at the selected dose level, doses of 400 and 800 mg venetoclax once daily were selected, which were

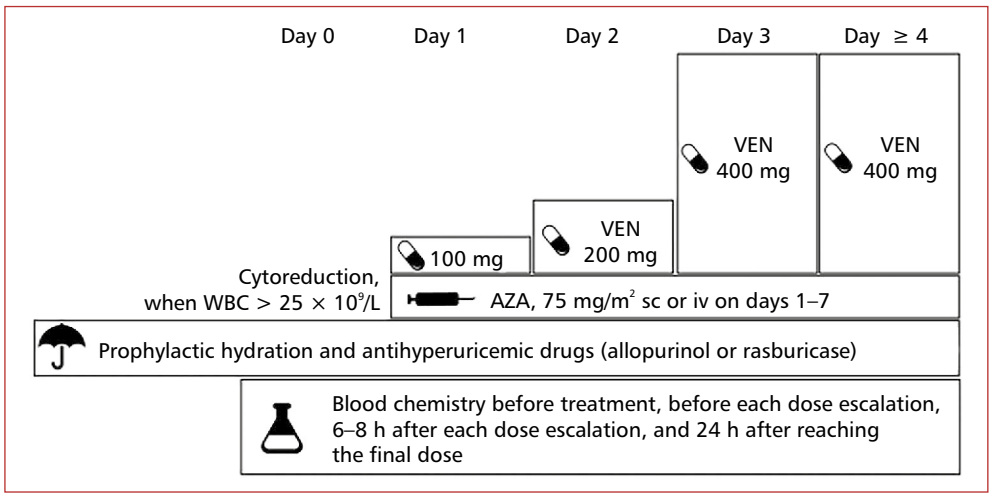

Figure 1. Dose titration schedule for venetoclax (VEN) in combination with azacitidine (AZA) and prevention of tumour lysis syndrome; WBC — white blood cell count; sc — subcutaneous; iv — intravenous

combined with AZA 75 mg/m^2 administered from day 1 to 7 of the cycle or with decitabine 20 mg/m^2 on days 1–5 of the cycle. Combination therapy was well tolerated and the most frequently observed adverse events were haematological and gastrointestinal toxicity. The most common grade 3 and 4 adverse events were febrile neutropenia (43%), leukopenia (31%), anaemia (25%), thrombocytopenia (24%), neutropenia (17%) and pneumonia (13%). There was no high mortality rate during the first 30 days of therapy (3%) and the median number of treatment cycles was 5 (1–25). Complete remission (CR) and complete remission with incomplete count recovery (CRi) rate was 67% and the median time to response was 1.2 months. Negativization of measurable residual disease (MRD) was achieved in 29% of patients. Median OS in the intention-to-treat (ITT) population was 17.5 months [13]. These results indicated high clinical activity in terms of response rate, time to response and OS compared to historical data on HMA monotherapy [4, 5]. The confirmatory, randomized, double-blind VIALE-A study compared the efficacy and safety of venetoclax plus AZA with placebo plus AZA in a similar group of patients as in the phase Ib study [12].

VIALE-A study included 431 patients (286 in the venetoclax plus AZA group and 145 in the placebo plus AZA group) with newly diagnosed AML, intermediate and high cytogenetic risk, who were ineligible for intensive chemotherapy due to age (> 75 years) or presence of one of the following conditions/co-morbidities: treated congestive heart failure, left ventricular ejection fraction < 50%, stable chronic angina pectoris, diffusion lung capacity ≤ 65%, forced expiratory volume in 1 second (FEV_1) ≤ 65%, performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) scale 2 or 3. All patients received tumour lysis syndrome (TLS) prophylaxis, including hyperuricemia preventive drugs and adequate hydration [oral or intravenous (iv)]. In total 82% of patients received anti-infective prophylaxis. Patients in the experimental group started with a 3-day daily titration protocol to reach the target dose of 400 mg venetoclax once daily (Figure 1). In subsequent cycles, venetoclax was administered at a dose of 400 mg once daily. AZA was administered iv or subcutaneously (sc) at a dose of 75 mg/m^2 on days 1–7 every 28-day cycle (Figure 1). Patients continued treatment in cycles until disease progression or unacceptable toxicity occurrence. The primary endpoint was OS. Overall, the median follow-up (range) was 20.5 months (< 0.1–30.7 months). The median duration of treatment in the venetoclax + AZA combination group was 7 cycles compared to 4.5 cycles in the control group. Venetoclax with AZA was more effective than AZA monotherapy (Table 1). Treatment with venetoclax plus AZA led to rapid and sustained remission (43% of patients achieved CR/CRi by the start of cycle 2). The CR/CRi rate in the venetoclax plus AZA group was significantly higher in the subgroups of patients with intermediate and high cytogenetic risk, newly diagnosed and secondary AML, and AML with high-risk mutations (e.g. *TP53, FLT3*, *IDH1* or *IDH2* genes) than in patients treated with AZA in the control arm. Subgroup analysis showed an

Table 1. Efficacy outcomes in the VIALE-A study

Evaluated parameter	VEN + AZA (n = 286)	PBO + AZA (n = 145)	p value
OS, median (95% CI), years	14.7 (11.9–18.7)	9.6 (7.4–12.7)	< 0.001
CR/CRi, % (95% CI)	66.4 (60.6–70.2)	28.3 (21.1–36.3)	< 0.001
Time to CR/CRi, median (95% CI), months	1.3 (0.6–9.9)	2.8 (0.8–13.2)	
Duration of CR/CRi, median (95% CI), months	17.5 (13.6–NR)	13.4 (5.8–15.5)	

VEN — venetoclax; AZA — azacitidine; PBO — placebo; OS — overall survival; CI — confidence interval; CR — complete remission; CRi — complete remission with incomplete count recovery; NR — no reached

OS benefit; mainly in groups with newly diagnosed and secondary AML, in patients with intermediate cytogenetic risk and with *IDH1* or *IDH2* gene mutations. However, the results of additional analyses should be interpreted with caution, as the number of some subgroups was small [12]. In addition, a pooled analysis of data from the early and late phase studies of the venetoclax/azacitidine regimen showed that the increased remission rate achieved with treatment did not always translate to improved duration of response and OS, especially in patients with high-risk cytogenetic abnormalities and *TP53* mutations [12, 26].

The adverse reactions observed in the study were consistent with the known toxicity profiles of AZA and venetoclax as well as those observed in the earlier phase studies. The most common treatment-related adverse events were gastrointestinal and haematological disorders, with a higher incidence of neutropenia and febrile neutropenia in the venetoclax plus AZA group than in the AZA monotherapy group. The rate of treatment interruptions due to haematological toxicity was higher in the venetoclax plus AZA group than in the AZA monotherapy group, but this did not translate to more frequent treatment discontinuations or dose reductions. In the VIALE-A study, 24% of patients discontinued treatment with venetoclax in combination with AZA due to adverse events, compared to 20% in the group treated with AZA. In total 72% of patients treated with venetoclax plus AZA had breaks between successive cycles due to adverse events, and 3% of patients received venetoclax in reduced doses. Breaks between and during cycles were mainly due to febrile neutropenia (21%), neutropenia (19%) and thrombocytopenia (10%). The quality of life was similar in both study groups [12].

Safety and adverse events management

Venetoclax in combination with AZA is a therapy that requires attention and consistency. The beginning of therapy requires an assessment of TLS risk and appropriate prophylaxis. Despite the unprecedentedly high effectiveness of therapy in this difficult-to-treat group of patients, adverse events may lead to premature treatment discontinuation and reduction of the chance to achieve remission. In addition, as venetoclax is primarily metabolized by CYP3A, it may interact with other agents metabolized by this enzyme system, including drugs commonly used to prevent infection in AML patients. In case of concomitant use of such drugs, the dosage of venetoclax should be adjusted accordingly. Below are practical guidelines for initiating therapy, cytopenia management and the risk of venetoclax drug interactions.

Treatment initiation and tumour lysis syndrome prevention

From experience in the treatment of CLL patients, it is known that venetoclax can cause a rapid reduction of the tumour mass and increases the risk of TLS [27, 28]. As in patients with CLL, in the treatment of AML with venetoclax, prophylactic measures and careful monitoring are necessary to prevent rapid tumour lysis.

There were rare cases of TLS in clinical trials with venetoclax for the treatment of AML; no TLS was reported in the venetoclax/decitabine efficacy study [13] and the VIALE-A study, in the first days of therapy, TLS occurred only in 3 patients (1%) and no cases were reported in the group treated with AZA alone [12]. No cases of clinically symptomatic TLS were reported in the phase II VIALE-C study, and in two patients (2.4%) with electrolyte disturbances and elevated uric acid level dose escalation was safely performed [19]. Many researchers believe that in real clinical practice, TLS in patients treated with venetoclax and AZA is more common than in clinical trials, and prophylaxis, which was the standard in each study, is sometimes underestimated. Keruakous et al. [29] reported 14 cases of TLS associated with treatment with venetoclax and AZA, despite the use

of prophylaxis as described in the studies. Events occurred more frequently in patients using azole derivatives for the prophylaxis of fungal infections. Esparza et al. [30] reported 3 cases of TLS associated with the use of venetoclax in AML therapy, which accounted for 7% of all patients treated in the centre (n = 45), and Huang et al. [31] reported 4 cases, which accounted for 3% of all analysed patients (n = 121). Although the incidence of TLS is low in clinical practice, it appears to be higher than in clinical trials and varies between centres, which may indicate differences in the standard of care or risk assessment.

Treatment with venetoclax should be initiated in the hospital setting. To reduce the risk of TLS during cycle 1, the dose of venetoclax should be escalated gradually (so-called dose-titration) starting with 100 mg on day 1, 200 mg on day 2, and 400 mg on day 3 and subsequent days until day 28 (Figure 1) [12]. This basic titration regimen may change, e.g. if there is a need to co-administer drugs that interact with venetoclax. In patients with a white blood cell count $> 25 \times 10^9$/L before initiation of venetoclax treatment, cytoreductive treatment with hydroxycarbamide is recommended. All patients, regardless of uric acid blood levels, receive anti-hyperuricemic prophylaxis before and during venetoclax dose escalation. For this purpose, allopurinol, a xanthine oxidase inhibitor, is administered, which, due to its mechanism of action, requires several days of use to effectively reduce the concentration of uric acid. Unlike allopurinol, the use of rasburicase, a recombinant urate oxidase, gives an immediate effect and additionally does not require dose adjustment in patients with renal failure [32]. All patients should be adequately hydrated before initiation of venetoclax therapy, either orally or intravenously, and adequate fluid intake should be ensured during the titration period and for 24–48 h after initiation of stable dosing. Laboratory parameters of TLS (potassium, uric acid, phosphorus, calcium and creatinine) should always be assessed before initiation of treatment and any abnormalities should be corrected. These parameters should be monitored every 6–8 h after each new dose, up to 24 hours after the first dose of 400 mg [33]. In patients with risk factors for TLS (blood circulating blasts, large tumour burden, elevated lactate dehydrogenase levels, or renal failure), the frequency of monitoring laboratory test results should be further increased. The use of venetoclax with drugs that inhibit CYP3A requires special attention, among others due to the risk of TLS, and therefore a separate chapter is devoted to this issue.

Cytopenias

Cytopenias are common in AML patients; in the VIALE-A study 31%, 51%, and 72% of patients had grade ≥ 3 anaemia, thrombocytopenia, and neutropenia, respectively, before initiation of venetoclax plus AZA. Patients with AML who have previously been diagnosed with myelodysplastic syndrome (MDS) are particularly at risk of cytopenias [34]. During treatment with venetoclax and AZA cytopenias grade ≥ 3 were observed in 82% of patients vs. 68% in the AZA group. Severe adverse events, such as febrile neutropenia, were reported twice as often in the venetoclax plus AZA group than in the AZA group (42 *vs.* 19%) [12]. Such a high incidence of haematological adverse events requires appropriate management to maintain treatment continuity.

Management of grade 4 cytopenia depends on disease status. This means the need for an early bone marrow assessment, preferably at 21–28 days of cycle 1; the result allows choosing of an appropriate strategy. Making the right decision is very important because effective and appropriate long-term administration of the drug in the initial stage creates optimal chances to achieve complete remission. Therefore, if blasts are still present in early bone marrow evaluation, treatment should not be discontinued for isolated grade 4 cytopenia (Table 2). The patient should be closely monitored for the presence of fever or other signs of infection. These symptoms are an indication for further treatment in a hospital and for considering interruption of treatment with venetoclax. Anaemia and thrombocytopenia, which are commonly observed, require transfusions of red blood cells or platelet concentrate in a hospital setting and the use of appropriate supportive care.

Composite complete remission was achieved in 66.4% of the patients in the registration study, and the majority of patients (43,4%) achieved CR at the end of the first treatment cycle [12]. In addition a subanalysis of this study showed that up to 77% of patients achieved blast clearance (< 5%) after the first cycle of treatment [35]. Elimination of blasts from the bone marrow, or achieving at least a leukaemia-free morphological status in the case of cytopenia, is an indication for treatment interruption, and its resumption when the morphology recovers (Figure 2). Making such a decision requires an assessment of response to treatment, which is usually performed on day 28 of cycle 1, but may be considered earlier, e.g. on day 21 of the cycle, especially when fever or

Table 2. Venetoclax dose modification for the management of grade 4 cytopenia during the treatment of newly diagnosed acute myeloid leukaemia

Time of cytopenia onset	Management
Before achieving remission	Do not stop treatment. Consider evaluation of bone marrow cellularity in patients with fever or symptoms of infection to decide on further treatment. Use transfusions and appropriate supportive care
First cytopenia after remission	Defer the next cycle and monitor blood parameters. Consider G-CSF for neutropenia. After the resolution to grade 1 or 2, resume venetoclax at the previous dose
Another cytopenia after achieving remission	Defer the next cycle and monitor blood parameters. Consider G-CSF for neutropenia. After the resolution to grade 1 or 2, resume venetoclax at the previous dose, reducing the duration of venetoclax administration by 7 days in each subsequent cycle (to 21 days instead of 28 days). Modify the dose of AZA depending on the time it took to recover (≤ or > 14 days).

AZA — azacitidine; G-CSF — granulocyte-colony stimulating factor

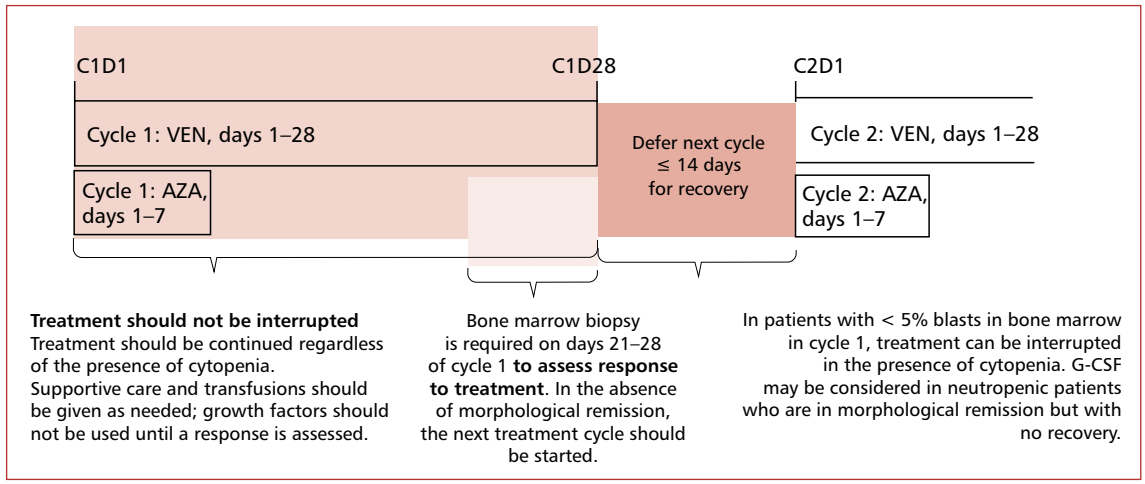

Figure 2. Scheme of management during the first cycle of venetoclax (VEN) with azacitidine (AZA) therapy. In the case of cytopenias, a bone marrow assessment should be performed at the end of cycle 1, which will make it possible to decide whether to interrupt therapy for the duration of bone marrow regeneration; G-CSF — granulocyte-colony stimulating factor

symptoms of infection appear during treatment (Figure 2). Earlier confirmation of treatment response makes it possible to defer the next cycle of therapy (Figure 2). In the VIALE-A study, 75% of patients who achieved remission had the next cycle of therapy deferred, and the median (range) delay in starting the next cycle was 9 days (1–39) [35]. In patients with bone marrow blast reduction who do not meet the criteria for remission after the first cycle and without recovery, the next treatment cycle should be started as scheduled. Treatment interruption could possibly reduce the chance to achieve remission. The impact of cytopenias, delays and interruptions in venetoclax administration on treatment efficacy is under ongoing studies. In the case of post-remission neutropenia, treatment with granulocyte-colony stimulating factors (G-CSF) may be considered to accelerate regeneration. This topic will be developed later in this chapter.

Cytopenias are also common after achieving remission. In the VIALE-A study, after-remission cytopenias occurred in 87% of patients treated with venetoclax plus AZA and 48% of patients treated with AZA alone [35]. If grade 4 cytopenia develops on treatment in a patient who has previously achieved remission, venetoclax should be interrupted and blood counts monitored. When the first cytopenia after remission lasts at least 7 days, venetoclax may be resumed at the previous dose after recovery to grade 1 or 2. Recurrence of cytopenias lasting 7 days or more requires interruption of venetoclax, and upon resolution or improvement to grade 1 or 2, re-initiation of treatment

at the previous dose but reducing the duration of venetoclax administration by 7 days, i.e. 21 days in a cycle of 28 days. Treatment with azacitidine in the case of cytopenias should be adapted according to Summary of Product Characteristics (SmPC). If morphology recovery was achieved within 14 days, AZA can be used in the next cycle at the standard dose, and if the time to recovery was > 14 days, the dose of AZA should be reduced [36]. Among responding patients, the median duration of delay in starting the next cycle was 14 days in the venetoclax plus AZA group and 11 days in the AZA monotherapy group. The dosing intervals during an ongoing cycle were significantly shorter than the next cycle deferring; the median duration of dosing intervals during a treatment cycle was 2 days in the venetoclax and AZA group and 1 day in the AZA group [35].

G-CSF should be considered for the treatment of post-remission neutropenia. The use of G-CSF in AML requires an individual assessment of benefits and risks, as blasts may possess cytokine--interacting receptors, which may potentially lead to the proliferation of leukemic cells [37, 38]. However, the risk of recurrence must be balanced with the risk of infectious complications and their consequences. Given that treatment with venetoclax with AZA increases the chances to achieve sustained remissions, supportive treatment with G-CSF to increase exposure to primary therapy may be appropriate. Almost every fourth patient (23%) achieving remission in the VIALE-A trial needed to receive ≥ 2 cycles of venetoclax plus AZA before achieving disease remission. On the other hand, the elimination of blasts found in bone marrow assessment indicates that the treatment is moving towards remission, allowing recovery at a natural pace, which should not be speeded up. In such cases, it seems reasonable to administer G-CSF only in the case of prolonged neutropenia increasing the risk of infectious complications [39]. The decision to use G-CSF should be made based on the physician's experience and a detailed analysis of the clinical situation, considering the following principles for the treatment of neutropenia in the course of venetoclax plus AZA therapy with G-CSF:

- the use of G-CSF as a prophylactic therapy is not recommended;
- the use of G-CSF is not recommended if blast clearance in the bone marrow has not occurred;
- G-CSF should not be used during the first treatment cycle, i.e. between days 1 and 28 of cycle 1;
- G-CSF should not be administered in patients with prolonged neutropenia who are in good general condition without signs of infection and fever.

Isolated neutropenia during venetoclax therapy is not an indication of hospitalization. Outpatient treatment reduces the risk of infections with resistant nosocomial pathogens that are difficult to treat. This supports the discharge of patients who are fever-free and in good general condition, without infection. It is worth taking into account the conditions of the patient's home environment, e.g. the number of cohabitants and their degree of vaccination against infectious diseases. In the beginning, follow-up visits should take place once a week, but the frequency of visits should depend on the blood count results. Patients with fever and symptoms of infection should be admitted to haematology departments. The above recommendations are based on data from the pivotal study, where the percentage of patients who developed serious infections was similar in the group treated with venetoclax plus AZA and AZA alone (pneumonia, 17% and 22%, respectively, and septic shock, 6% and 8%, respectively) [12].

Interactions with other drugs

Invasive fungal disease (IFD), mainly invasive aspergillosis, is a serious problem among patients receiving intensive chemotherapy for acute leukaemias [40]. In the past two decades of the 21st century, significant progress has been made in preventing infections and reducing mortality, including with the prophylactic use of posaconazole [41]. It is a treatment with a proven beneficial effect on the overall survival of AML patients [42, 43]. American studies have confirmed that other drugs from the azole group are also effective in IFD prevention [44].

As venetoclax is a substrate of the CYP3A enzyme, its concomitant use with CYP3A inhibitors or inducers may result in changes in venetoclax concentration and exposure, which may affect the efficacy and safety of the therapy. In early clinical trials, venetoclax was administered at doses up to 1200 mg daily, however, at doses > 400 mg, haematological toxicity outweighed the clinical benefit [13]. Therefore, venetoclax dose reduction is necessary when there is a risk of interactions that may result in increased venetoclax exposure, e.g. with CYP3A inhibitors [45]. Such drugs include azoles commonly used in IFD prevention and treatment, including the previously mentioned

Table 3. Some medicinal products interacting with venetoclax by the mechanism of interaction and potency

Interaction mechanism and impact strength	Products
Strong CYP3A inhibitor	Clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, posaconazole, ritonavir, telaprevir, voriconazole
Moderate CYP3A inhibitor	Ciprofloxacin, diltiazem, erythromycin, fluconazole, verapamil, grapefruit, bitter orange, starfruit
Moderate CYP3A inducer	Bosentan, efavirenz, etravirine, modafinil, nafcillin
Strong CYP3A inducer	Carbamazepine, phenytoin, rifampicin, St. John's wort
P-glycoprotein inhibitor	Rifampicin
P-glycoprotein and BCRP substrates	Digoxin, dabigatran, everolimus, sirolimus
OATP substrates	Statins

BCRP — breast cancer resistance protein; CYP3A — cytochrome P450, family 3 subfamily A; OATP — organic anion transporting polypeptide 1B1

and used as the drug of choice posaconazole [46] (Table 3). Administration of posaconazole, a potent CYP3A inhibitor, increased the peak venetoclax concentration by approximately 2-fold and the area under the concentration-time curve by as much as 2.5-fold. To treat effectively and safely, the dose of venetoclax must be reduced by 75% when co-administered with posaconazole [21, 46] Particular attention should be paid to the venetoclax titration period when strong CYP3A inhibitors are co-administered; 10 mg is administered on day 1, 20 mg on day 2, 50 mg on day 3 and maximum 100 mg on day 4. This also applies to voriconazole — when used concomitantly, the dose of venetoclax should be reduced to 100 mg or less (or by ≥ 75%) if it has already been adjusted for other reasons [21].In the case of moderate CYP3A inhibitors (Table 3), at least a 50% reduction of venetoclax dose is required [21]. Venetoclax at the dose used before initiation of the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor.

Clinical centres increasingly use the monitoring of venetoclax and/or posaconazole concentrations, however, due to the limited access to this type of laboratory tests, reliance should be placed on the results of pharmacokinetic studies and recommendations on drug combinations formulated on their basis [21]. Interactions between venetoclax and CYP3A inhibitors (Table 3) may have adverse consequences, such as TLS [29] or prolongation of thrombocytopenia recovery [47]. On the other hand, the concomitant use of enzyme inducers (Table 3) may limit the effectiveness of treatment. Table 1 lists drugs that interact with venetoclax, including P-glycoprotein inhibitors and substrates, breast cancer resistance protein (BCRP) and organic anion transporting polypeptide 1B1 (OATP1B1), which are also involved in venetoclax metabolism *in vitro* [48]. This is a very diverse group of drugs, including drugs with a narrow therapeutic index and widely used drugs. Therefore, patients treated with venetoclax should be under the supervision of a pharmacist to ensure that drugs or dietary supplements that affect the metabolism of venetoclax are not administered without proper monitoring. Unfortunately, both access to pharmaceutical care and physicians' knowledge about the interaction of drugs used in outpatient clinics and drug programs is limited. Therefore, it is necessary to inform and issue written recommendations regarding the applied treatment for both patients and general practitioners.

Considering the above-mentioned drug interactions, it should be considered whether each AML patient treated with venetoclax requires antifungal prophylaxis with azole derivatives. In a retrospective real-world clinical study, the rate of probable fungal infections in newly diagnosed AML patients treated with venetoclax and HMA was 5%. IFDs were significantly more common in non-responders and those with refractory and relapsing disease. In this study, prophylaxis with micafungin was used in 38% of patients and with azoles in 41% of patients, and no antifungal prophylaxis was used in the remaining patients. The age of patients, type of HMA and duration of neutropenia have not been shown to influence the incidence of IFD [49]. The authors believe that in patients with newly diagnosed AML qualified for treatment with venetoclax in combination with HMA, the routine use of prophylactic antifungal treatment is not justified, except for patients at high risk of infection. In the VIALE-A study, azoles were administered in 36% of patients in the study group, while echinocandins (caspofungin and micafungin) were used in 15% of patients [12]. Currently, there is no information on

the effectiveness of using venetoclax in reduced doses, therefore it is recommended, if possible, to avoid drug-drug interactions, including unjustified antifungal prophylaxis in patients with newly diagnosed AML qualified for treatment with venetoclax and AZA. If antifungal prophylaxis is necessary, it is recommended to use drugs non-metabolised by cytochrome P450.

According to the European Haematology Association (EHA), the certainty of the evidence supporting the use of antifungal prophylaxis in patients with AML treated with venetoclax is low. The EHA recommends limiting antifungal prophylaxis, primarily with azoles, to patients at high risk of IFD, e.g. patients with long-term neutropenia. Accordingly, the decision on prophylactic pharmacotherapy should be made in the context of individual patients, treatment history and environmental conditions. The EHA recommends reducing the dose of venetoclax with concomitant use of azoles by at least 75% and taking special care during breaks in prophylaxis and when there are disturbances in the absorption of the antifungal drug, carrying the risk of non-therapeutic concentration of venetoclax [50].

Summary

The results of therapy in patients with AML not eligible for intensive treatment have so far been unsatisfactory. Combination therapy of venetoclax with HMA has increased the number of treatment options available to patients in this difficult-to-treat group and significantly improved the prognosis. Thus, a new standard of care was established, the use of which allows for achieving higher rates of remission and prolonging survival. Venetoclax in combination with AZA is the only treatment regimen for newly diagnosed AML for which there is clinical evidence from a phase III randomized trial [12] and real-world clinical trials [51].

The main challenge during therapy with venetoclax plus AZA is myelosuppression, which may also occur in patients after achieving remission. Most patients require venetoclax and/or AZA dose modifications, usually prolongation the intervals between cycles, but also treatment interruptions during the cycle. Treatment with venetoclax requires attention and consistency, and too hasty therapy discontinuation may reduce the chances to achieve remission. (Table 1). Moreover 23,4% (67/286) of all patients treated with venetoclax plus AZA achieved MRD negativization and related additional benefits in terms of OS [52]. Therefore, it is recommended to not interrupt or modify the doses until remission is achieved. Once remission is achieved, modification of the duration of venetoclax dosing (21 days instead of 28 days) is preferable to dose reduction. Approximately 14-day intervals between treatment cycles seem reasonable to allow for recovery from treatment-induced cytopenia [53]. In the case of prolonged neutropenia, the use of G-CSF may be considered, especially if infectious complications occur.

Treatment with venetoclax requires dose adjustments depending on the concomitant medications that may interact. This applies to e.g. azole derivatives used in the prophylaxis of IFD. Due to the limited knowledge of the effectiveness of reduced doses of venetoclax and the relatively low risk of fungal infections in patients treated with venetoclax with AZA compared to those treated with intensive chemotherapy, it seems that antifungal prophylaxis should be limited only to selected patients at risk of infection. Knowledge of the use of venetoclax in AML therapy will certainly be expanded in the coming years.

Acknowledgements

This article is based on the authors' feedback and discussion at an advisory committee meeting hosted by AbbVie. The publication has been prepared solely by its authors, without substantive interference in its content. Editorial assistance provided by Unique Work S.A. funded by AbbVie.

Conflict of interest

SG provided consultancy services and is part of the speakers' bureaus (AbbVie and BMS). GH participated in the advisory board (AbbVie). TW received honoraria, participated in advisory boards (AbbVie, Janssen-Cilag, Roche, and AstraZeneca) and received research support (Roche). JMZ participated in advisory boards (AbbVie, Takeda, Roche, Novartis, and Astellas). BB provided consultancy services (AbbVie). AW fee for the advisory role (AbbVie, Astellas, BMS, Celgene, Gilead, Janssen-Cilag, Jazz Pharmaceuticals, Novartis, Servier), financing of clinical trials (Jazz Pharmaceuticals). LG gave lectures for AbbVie, Novartis, Astellas, BMS and Pfizer and participated in advisory meetings: AbbVie, Astellas, and BMS. AS gave lectures for AbbVie, Novartis.

References

1. Seferyńska I, Warzocha KA. Raport z rejestru zachorowań na ostre białaczki u osób dorosłych w Polsce w latach 2004–2010 prowadzonego przez Instytut Hematologii i Transfuzjologii w imieniu Polskiej Grupy ds. Leczenia Białaczek u Dorosłych (PALG). Hematologia. 2014; 5(2): 162–72.
2. Dong Y, Shi O, Zeng Q, et al. Leukemia incidence trends at the global, regional, and national level between 1990 and 2017. Exp Hematol Oncol. 2020; 9: 14, doi: 10.1186/s40164-020-00170-6, indexed in Pubmed: 32577323.
3. Rücker FG, Schlenk RF, Bullinger L, et al. TP53 alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. Blood. 2012; 119(9): 2114–2121, doi: 10.1182/blood-2011-08-375758, indexed in Pubmed: 22186996.
4. Dombret H, Seymour JF, Butrym A, 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(3): 291–299, doi: 10.1182/blood-2015-01-621664, indexed in Pubmed: 25987659.
5. Kantarjian HM, Thomas XG, Dmoszynska A, 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; 30(21): 2670–2677, doi: 10.1200/JCO.2011.38.9429, indexed in Pubmed: 22689805.
6. Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. Cancer. 2007; 109(6): 1114–1124, doi: 10.1002/cncr.22496, indexed in Pubmed: 17315155.
7. Burnett AK, Hills RK, Hunter AE, et al. UK National Cancer Research Institute AML Working Group. The addition of gemtuzumab ozogamicin to low-dose Ara-C improves remission rate but does not significantly prolong survival in older patients with acute myeloid leukaemia: results from the LRF AML14 and NCRI AML16 pick-a-winner comparison. Leukemia. 2013; 27(1): 75–81, doi: 10.1038/leu.2012.229, indexed in Pubmed: 22964882.
8. Sekeres MA, Lancet JE, Wood BL, et al. Randomized phase IIb study of low-dose cytarabine and lintuzumab versus low-dose cytarabine and placebo in older adults with untreated acute myeloid leukemia. Haematologica. 2013; 98(1): 119–128, doi: 10.3324/haematol.2012.066613, indexed in Pubmed: 22801961.
9. Zeidan AM, Boss I, Beach CL, et al. A randomized phase 2 trial of azacitidine with or without durvalumab as first-line therapy for older patients with AML. Blood Adv. 2022; 6(7): 2219–2229, doi: 10.1182/bloodadvances.2021006138, indexed in Pubmed: 34933333.
10. Saxena K, Herbrich SM, Pemmaraju N, et al. A phase 1b/2 study of azacitidine with PD-L1 antibody avelumab in relapsed/refractory acute myeloid leukemia. Cancer. 2021; 127(20): 3761–3771, doi: 10.1002/cncr.33690, indexed in Pubmed: 34171128.
11. Duong VuH, Ruppert A, Mims A, et al. Entospletinib (ENTO) and decitabine (DEC) combination therapy in older newly diagnosed (ND) acute myeloid leukemia (AML) patients with mutant TP53 or complex karyotype is associated with poor response and survival: a phase 2 sub-study of the beat AML master trial. Blood. 2021; 138(Suppl 1): 1279–1279, doi: 10.1182/blood-2021-151234.
12. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020; 383(7): 617–629, doi: 10.1056/NEJMoa2012971, indexed in Pubmed: 32786187.
13. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2019; 133(1): 7–17, doi: 10.1182/blood-2018-08-868752.
14. Pratz KW, Panayiotidis P, Recher C, et al. Venetoclax combinations delay the time to deterioration of HRQoL in unfit patients with acute myeloid leukemia. Blood Cancer J. 2022; 12(4): 71, doi: 10.1038/s41408-022-00668-8, indexed in Pubmed: 35443742.
15. Kapoor I, Bodo J, Hill BT, et al. Targeting BCL-2 in B-cell malignancies and overcoming therapeutic resistance. Cell Death Dis. 2020; 11(11): 941, doi: 10.1038/s41419-020-03144-y, indexed in Pubmed: 33139702.
16. Konopleva M, Pollyea DA, Potluri J, et al. Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. Cancer Discov. 2016; 6(10): 1106–1117, doi: 10.1158/2159-8290.CD-16-0313, indexed in Pubmed: 27520294.
17. Teh TC, Nguyen NY, Moujalled DM, et al. Enhancing venetoclax activity in acute myeloid leukemia by co-targeting MCL1. Leukemia. 2018; 32(2): 303–312, doi: 10.1038/leu.2017.243, indexed in Pubmed: 28751770.
18. Bogenberger JM, Delman D, Hansen N, et al. Ex vivo activity of BCL-2 family inhibitors ABT-199 and ABT-737 combined with 5-azacytidine in myeloid malignancies. Leuk Lymphoma. 2015; 56(1): 226–229, doi: 10.3109/10428194.2014.910657, indexed in Pubmed: 24707940.
19. Wei AH, Strickland SA, Hou JZ, et al. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study. J Clin Oncol. 2019; 37(15): 1277–1284, doi: 10.1200/JCO.18.01600, indexed in Pubmed: 30892988.
20. VENCLEXTA (venetoclax). U.S. Food and Drug Administration. Apr 11, 2016. https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=208573# (August 22, 2022).
21. Venclyxto. Summary of Product Characteristics. European Medicines Agency, 2016. https://www.ema.europa.eu/en/medicines/human/EPAR/venclyxto (August 22, 2022).
22. Pan R, Hogdal LJ, Benito JM, et al. Selective BCL-2 inhibition by ABT-199 causes on-target cell death in acute myeloid leukemia. Cancer Discov. 2014; 4(3): 362–375, doi: 10.1158/2159-8290.CD-13-0609, indexed in Pubmed: 24346116.
23. Campos L, Rouault JP, Sabido O, et al. High expression of bcl-2 protein in acute myeloid leukemia cells is associated with poor response to chemotherapy. Blood. 1993; 81(11): 3091–3096, indexed in Pubmed: 7684624.
24. Jin S, Cojocari D, Purkal JJ, et al. 5-azacitidine induces NOXA to prime AML cells for venetoclax-mediated apoptosis. Clin Cancer Res. 2020; 26(13): 3371–3383, doi: 10.1158/1078-0432.CCR-19-1900, indexed in Pubmed: 32054729.
25. Bose P, Gandhi V, Bose P, et al. Pathways and mechanisms of venetoclax resistance. Leuk Lymphoma. 2017; 58(9): 1–17, doi: 10.1080/10428194.2017.1283032, indexed in Pubmed: 28140720.
26. Pollyea DA, Pratz KW, Wei AH, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. Lancet Oncol. 2018; 19(2): 216–228, doi: 10.1016/S1470-2045(18)30010-X, indexed in Pubmed: 29339097.
27. Gribben JG. Practical management of tumour lysis syndrome in venetoclax-treated patients with chronic lymphocytic leukaemia. Br J Haematol. 2020; 188(6): 844–851, doi: 10.1111/bjh.16345, indexed in Pubmed: 31858596.
28. Iskierka-Jażdżewska E, Robak T. Minimizing and managing treatment-associated complications in patients with chronic lympho-

cytic leukemia. Expert Rev Hematol. 2020; 13(1): 39–53, doi: 10.1080/17474086.2020.1696185, indexed in Pubmed: 31747803.
29. Keruakous A, Saleem R, Asch A. Venetoclax-induced tumor lysis syndrome in acute myeloid leukemia: real world experience. J Clin Oncol. 2020; 38(15_suppl): e19542–e19542, doi: 10.1200/jco.2020.38.15_suppl.e19542.
30. Esparza S, Muluneh B, Galeotti J, et al. Venetoclax-induced tumour lysis syndrome in acute myeloid leukaemia. Br J Haematol. 2020; 188(1): 173–177, doi: 10.1111/bjh.16235, indexed in Pubmed: 31621058.
31. Huang JQ, Academia E, Pollyea DA, et al. Tumor lysis syndrome (TLS) in acute myeloid leukemia (AML) patients treated with azacitidine (AZA) and venetoclax (VEN). J Clin Oncol. 2020; 38(15_suppl): e19507–e19507, doi: 10.1200/jco.2020.38.15_suppl.e19507.
32. Matuszkiewicz-Rowinska J, Malyszko J. Prevention and treatment of tumor lysis syndrome in the era of onco-nephrology progress. Kidney Blood Press Res. 2020; 45(5): 645–660, doi: 10.1159/000509934, indexed in Pubmed: 32998135.
33. 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, doi: 10.1177/2040620719882822, indexed in Pubmed: 31692757.
34. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012; 120(12): 2454–2465, doi: 10.1182/blood-2012-03-420489, indexed in Pubmed: 22740453.
35. Pratz KW, DiNardo CD, Selleslag D, et al. Cytopenia management in patients with newly diagnosed acute myeloid leukemia treated with venetoclax plus azacitidine in the VIALE-A study. Blood. 2020; 136(Suppl 1): 51–53, doi: 10.1182/blood-2020-134832.
36. Vidaza. Summary of Product Characteristics. European Medicines Agency 2009. https://www.ema.europa.eu/en/medicines/human/EPAR/vidaza (August 22, 2022).
37. Czerw T, Labopin M, Gorin NC, et al. Use of G-CSF to hasten neutrophil recovery after auto-SCT for AML is not associated with increased relapse incidence: a report from the Acute Leukemia Working Party of the EBMT. Bone Marrow Transplant. 2014; 49(7): 950–954, doi: 10.1038/bmt.2014.64, indexed in Pubmed: 24710564.
38. Feng X, Lan He, Ruan Y, et al. Impact on acute myeloid leukemia relapse in granulocyte colony-stimulating factor application: a meta-analysis. Hematology. 2018; 23(9): 581–589, doi: 10.1080/10245332.2018.1446811, indexed in Pubmed: 29516766.
39. 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): 2795–2804, doi: 10.1038/s41375-019-0612-8.
40. Maertens JA, Girmenia C, Brüggemann RJ, et al. European Conference on Infections in Leukaemia (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 Immunocompromised Host Society (ICHS) and, European Conference on Infections in Leukaemia (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 Immunocompromised Host Society (ICHS) and the European LeukemiaNet (ELN). European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. J Antimicrob Chemother. 2018; 73(12): 3221–3230, doi: 10.1093/jac/dky286, indexed in Pubmed: 30085172.
41. Dragonetti G, Criscuolo M, Fianchi L, et al. Invasive aspergillosis in acute myeloid leukemia: are we making progress in reducing mortality? Med Mycol. 2017; 55(1): 82–86, doi: 10.1093/mmy/myw114, indexed in Pubmed: 27915304.
42. Pagano L, Caira M, Candoni A, et al. SEIFEM Group. Evaluation of the practice of antifungal prophylaxis use in patients with newly diagnosed acute myeloid leukemia: results from the SEIFEM 2010-B registry. Clin Infect Dis. 2012; 55(11): 1515–1521, doi: 10.1093/cid/cis773, indexed in Pubmed: 22955439.
43. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007; 356(4): 348–359, doi: 10.1056/NEJMoa061094, indexed in Pubmed: 17251531.
44. Barreto JN, Beach CL, Wolf RC, et al. The incidence of invasive fungal infections in neutropenic patients with acute leukemia and myelodysplastic syndromes receiving primary antifungal prophylaxis with voriconazole. Am J Hematol. 2013; 88(4): 283–288, doi: 10.1002/ajh.23388, indexed in Pubmed: 23460251.
45. Agarwal SK, Salem AH, Danilov AV, et al. Effect of ketoconazole, a strong CYP3A inhibitor, on the pharmacokinetics of venetoclax, a BCL-2 inhibitor, in patients with non-Hodgkin lymphoma. Br J Clin Pharmacol. 2017; 83(4): 846–854, doi: 10.1111/bcp.13175, indexed in Pubmed: 27859472.
46. Agarwal SK, DiNardo CD, Potluri J, et al. Management of venetoclax-posaconazole interaction in acute myeloid leukemia patients: evaluation of dose adjustments. Clin Ther. 2017; 39(2): 359–367, doi: 10.1016/j.clinthera.2017.01.003, indexed in Pubmed: 28161120.
47. Rausch CR, DiNardo CD, Maiti A, et al. Duration of cytopenias with concomitant venetoclax and azole antifungals in acute myeloid leukemia. Cancer. 2021; 127(14): 2489–2499, doi: 10.1002/cncr.33508, indexed in Pubmed: 33793970.
48. Weiss J, Gajek T, Köhler BC, et al. Venetoclax (ABT-199) might act as a perpetrator in pharmacokinetic drug-drug interactions. Pharmaceutics. 2016; 8(1), doi: 10.3390/pharmaceutics8010005, indexed in Pubmed: 26927160.
49. Aldoss I, Dadwal S, Zhang J, et al. Invasive fungal infections in acute myeloid leukemia treated with venetoclax and hypomethylating agents. Blood Adv. 2019; 3(23): 4043–4049, doi: 10.1182/bloodadvances.2019000930, indexed in Pubmed: 31816059.
50. Stemler J, de Jonge N, Skoetz N, et al. Antifungal prophylaxis in adult patients with acute myeloid leukaemia treated with novel targeted therapies: a systematic review and expert consensus recommendation from the European Hematology Association. Lancet Haematol. 2022; 9(5): e361–e373, doi: 10.1016/S2352-3026(22)00073-4, indexed in Pubmed: 35483397.
51. Heuser M, Ofran Y, Boissel N, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020; 31(6): 697–712, doi: 10.1016/j.annonc.2020.02.018, indexed in Pubmed: 32171751.
52. Pratz K, Jonas B, Pullarkat V, et al. Measurable residual disease response in acute myeloid leukemia treated with venetoclax and azacitidine. J Clin Oncol. 2021; 39(15_suppl): 7018, doi: 10.1200/jco.2021.39.15_suppl.7018.
53. Othman TA, Tenold ME, Moskoff BN, et al. Venetoclax-based combinations for the treatment of newly diagnosed acute myeloid leukemia. Future Oncol. 2021; 17(23): 2989–3005, doi: 10.2217/fon-2021-0262, indexed in Pubmed: 34024158.