Azacitidine Combined With Low Dose Venetoclax and Azole in Treatment-Naive, Elderly Patient with Acute Myeloid Leukemia: A Case Report

prefixed lower dose of 100 mg PO per day from day 1 to day 14, non-compliant with the current approved dosage. It was combined with Azacitidine 75 mg/m² per day from day 1 to day 7 and Fluconazole at a dose of 200 mg orally per day from day 1 to day 14. One cycle repeated every 28 days.

The patient was admitted to the hospital for the administration of Azacitidine for 7 days every cycle and for monitoring. Although he was at low risk of developing Tumor Lysis Syndrome (TLS), adequate hydration and uric acid lowering agents was administered. Progressively, the patient started showing clinical and hematological improvement with a clear decrease in transfusion needs.

A new bone marrow aspirate was done after 4 cycles showed a complete remission with slight dyserythropoiesis as well as complete hematologic remission. The Minimal Residual Disease (MRD) was not done since it was not available at our center (Figure 2).

Until the submission of the article the patient received a total of 6 cycles and still in complete remission.

Figure 2. Bone marrow aspirates showing complete remission with slight dyserythropoiesis.

Discussion

Low-dose Cytarabine (LDAC) and Hypomethylating Agents (HMA) such as Azacitidine or Decitabine have been the standard of care for elderly AML patient’s ineligible for intensive induction chemotherapy regimens. With low median survival rates, outcomes were still dismal [7].

Venetoclax, an oral and potent B-cell lymphoma 2 (BCL-2) inhibitor, when added to LDAC or HMA in frontline setting, demonstrated in a phase Ib study, published in 2019, an encouraging Overall Response Rate (ORR) of 68% and a leukemia response rate of 83% [8]. This was confirmed by the results of the phase III VIALE-A study in 2020 that showed a statistically significant improvement in overall survival and duration of remission when Venetoclax was added to Azacitidine in treatment-naive AML patients, ineligible for intensive therapy [9,10].

Venetoclax is metabolized mainly by the CYP3A4 enzyme and, to a lesser degree, by the p-glycoprotein. Therefore, its concomitant use with food or drugs that inhibit the CYP3A4 will increase its plasma concentration by 2 to 7 folds [10]. Fluconazole, a triazole antifungal drug commonly used in AML patients, is considered a moderate CYP3A4 inhibitor. When combined to Venetoclax, it increases the latter maximum concentration in the plasma as well as the Area under the Curve (AUC) by two to five folds prolonging the patient’s drug exposure [11]. That’s why it is recommended to reduce the dose of Venetoclax by around 50% when used in concomitance with Fluconazole to maintain safe therapeutic ranges preventing unwanted adverse events [7]. Moreover, Azacitidine metabolism is not mediated by the CYP enzymes; therefore, no effects were noticed when administered along with Fluconazole [12].

Based on Venetoclax pharmacokinetics and considering the inadequate accessible dose of Venetoclax by the patient’s third party (100 mg daily instead of 400 mg) along with the current Lebanese economic crisis that preclude additional cost on the patient, we decided to combine 200 mg of daily Fluconazole to the prefixed low dose Venetoclax in order to increase its bioavailability in the patient’s plasma and to increase his chance of response. This schema was extrapolated from the results of the phase lb sub-study evaluating Venetoclax with posaconazole interaction in untreated AML patients where the results showed an Overall Response Rate (ORR) of 67% [13]. Furthermore, the drug’s safety was comparable with no increased side effects related to the addition of CYP3A inhibitor as it was shown in the phase Ib/II study where 50% of the patients treated with Venetoclax combined to LDAC were receiving posaconazole [14]. In fact, the patient reached a complete remission upon the end of the fourth cycle. He presented grade I febrile neutropenia after the first two cycles treated adequately according to recommended protocols. No major adverse events were reported.

To date, we believe it’s the first case described in the literature, reporting a complete remission after combining low dose Venetoclax and Azacitidine to a moderate CYP3A4 inhibitor.

Conclusion

Venetoclax combined to HMA or LDAC increased the likelihood of achieving a complete remission in elderly AML patient ineligible for intensive therapies. However, access to costly oral drugs can financially exhausting the patient especially in countries facing economic crisis such as Lebanon. Our experience showed that adding a CYP3A4 inhibitor to Venetoclax at lower doses was as effective as treating the patient with the recommended ones. Thus, while decreasing the financial burden of the treatment, we tried to ensure, as much as possible, the same outcome and drug safety.

In the near future, with the rapid expansion of new innovative cancer drugs and their incorporation in the treatment guidelines, we will be concerned, as clinicians, on the burden of their cost and accessibility with their consequent financial toxicity on the patient. For that, we believe our case may open the floor for future prospective randomized clinical trials investigating the efficacy and tolerability of such combination.

References


