Clinical Oncology: Case Reports

Case Report

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Complete Remission of Acute Myeloid Leukemia in an Elderly Patient with a Single Dose of Venetoclax

Poornima Ramadas[1,2]* and David B Duggan[1]

Abstract

Treatment of Acute Myeloid Leukemia in older adults becomes challenging due to co-morbidities, poor functional status, higher incidence of unfavorable cytogenetics, and increased treatment resistance. Even though the overall survival in older patients with AML has historically remained poor, recent advances in treatment have resulted in improved survival in this population. Venetoclax, an oral BCL-2 inhibitor in combination with hypomethylating agents or low-dose cytarabine has been granted FDA approval for treatment of AML in patients who are 75 years or older or have co-morbid conditions that prohibit the use of intensive chemotherapy. This case report describes an elderly male patient who was diagnosed with AML and went into complete remission with a single dose of Venetoclax. Older patients who previously had high mortality due to the disease are now eligible for treatment with agents like Venetoclax with an acceptable toxicity profile. As we gain more understanding and experience with these newer drugs, a subset of patients could potentially be candidates for treatment with modified regimes which involves less drug exposure while maintaining remission and preserving the quality of life in the elderly population.

Keywords

Leukemia; Venetoclax; Myeloid

Background

Acute Myeloid Leukemia (AML) is the most common acute leukemia in adults with a median age of around 67 years at diagnosis with increasing incidence with age. Treatment of AML in older adults becomes challenging due to co-morbidities, poor functional status, higher incidence of unfavorable cytogenetics, and increased treatment resistance [1]. Despite this, treatment results in superior outcomes including symptom relief and improved quality of life compared with best supportive care [2,3]. Even though the overall survival in older patients with AML has historically remained poor, recent advances in treatment have resulted in improved survival in this population [3,4]. Azacitidine, decitabine, or low dose cytarabine are used in patients who are not candidates for intensive induction chemotherapy and have low response rates with only minimal improvement in survival [5-7]. Next-generation sequencing has helped identify novel molecular abnormalities associated with AML and to develop therapeutic targets. Venetoclax, an oral BCL-2 inhibitor in combination with hypomethylating agents or low-dose cytarabine has been granted FDA approval for treatment of AML in patients who are 75 years or older or have co-morbid conditions that prohibit the use of intensive chemotherapy [8].

We present a case of an elderly male patient who was diagnosed with AML and went into complete remission with a single dose of Venetoclax.

Case Presentation

86-year-old male with a long-standing history of giant cell arteritis on prednisone, gastroesophageal reflux disease, Raynaud's phenomenon, who was referred to hematology after he was noted to have pancytopenia on routine labs done by his rheumatologist. He was otherwise asymptomatic with good functional status. Initial labs showed White Blood Cell (WBC) count of 1.8 × 10^3/uL with Absolute Neutrophil Count (ANC) of 740/uL, Hemoglobin (Hb) of 11.2 g/dL and Platelets (Plt) of 81 × 10^3/uL. Bone marrow biopsy was done and revealed hypercellular marrow with 42% blasts, consistent with AML. Immunohistochemistry showed that the blasts were CD33, CD38, CD117, CD123, and myeloperoxidase positive; CD34 and CD13 were negative. Rapid FISH testing for t (15:17) was negative. Cytogenetics revealed normal karyotype and no evidence of Myelodysplastic Syndrome (MDS) associated abnormalities. He went for a second opinion at an outside hospital and underwent repeat bone marrow biopsy which again showed AML with trilineage dysplasia with 83% blasts on aspirate and 52% on flow cytometry. Molecular studies done showed positive IDH 1 Exon 4 R132 C mutation. Other studies including RUNX1T1-RUNX1 fusion t (8:21), MLL(11q23), CBFB(16q22), TP53(17p13.1), del17, FLT3 ITD, and FLT3 TKD were negative. Next-Generation Sequencing with PCR (Archer Fusionplex panel) was also negative. Decision was made to start treatment with Azacitidine with Venetoclax. He was started on Azacitidine at 75 mg/m^2 subcutaneous, which he received for two consecutive days. Labs on Day 1 of treatment showed WBC of 15.6 × 10^3/uL, ANC of 1090/uL with 58% blasts, Hb of 8.9 g/dL, and Plt of 43 × 10^3/uL. On Day 2, he received oral Venetoclax at 100 mg. He was admitted to the hospital the next day with neutropenic fever and was started on broad-spectrum antibiotics along with intravenous hydration. He was also noted to have acute kidney injury with a serum creatinine of 1.6 mg/dL on the second day of admission. Uric acid was also slowly noted to rise to a maximum of 7.4 mg/dL. Corrected calcium, phosphorous, and potassium levels remained stable. He also developed more pancytopenia with the lowest WBC counts of 0.4 × 10^3/uL, absolute neutrophil count of 20/uL, hemoglobin of 6.3 g/dL, and platelets of 13 × 10^3/uL. He had 6% blasts on the day of admission, which decreased to 2% on Day 3 of admission and was undetectable since then. He had intermittent fevers with no evidence of pathogen on cultures and was on prophylactic acyclovir and fluconazole along with antibiotic therapy. He required intermittent PRBC and platelet transfusions. Over the hospital course, as his counts slowly began recovering, he developed acute hypoxic respiratory failure. CT thorax done showed multifocal air space opacities. Pulmonary was consulted and he underwent a transbronchial biopsy which revealed acute lung injury with organizing pneumonia. He was started on high dose steroids and required a few days of ICU stay due to high oxygen requirements. He

***Corresponding author:** Poornima Ramadas, LSU Health Sciences Center, 1501 Kings Hwy, Shreveport, Louisiana, USA, E-mail: pra003@lsuhs.edu

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had a repeat bone marrow biopsy when his ANC was greater than 3000/uL and platelets were greater than 100 × 10^3/uL. Pathology revealed markedly hypocellular marrow with cytoreduction, morphology and flow cytometry with no evidence of increased blasts. Molecular studies showed continued positive IDH 1 mutation Exon 4R132 C mutation. He was discharged to a rehabilitation facility after 1.5 months of hospital stay. He gradually recovered back to his baseline. He remained in hematological remission for around 3 months, after which he had a repeat bone marrow biopsy which showed 8% blasts. Given his previous history of the above marked inflammatory reaction with treatment, he was treated with 7 days of Venetoclax 50 mg daily along with subcutaneous Azacitidine 75 mg/m^2, after which Venetoclax was held with neutropenia. He otherwise tolerated treatment well. He was continued on treatment at around 3-month intervals with 5 days of Venetoclax 50 mg and Azacitidine which kept his AML in remission till around 15 months after the initial diagnosis. Subsequently, he had relapse with bone marrow biopsy showing 26% blasts and was started on Ivosidenib 500 mg daily while continuing Azacitidine. He had some treatment response with a reduction of peripheral blast counts lasting for around 3 months. He continued to have prolonged cytopenias and underwent repeat bone marrow biopsy which showed persistent AML with 23.2% blasts and cytogenetics now showed deletion 13q. Decision was made to proceed with supportive care with transfusions and hydroxyurea as needed. Eventually, he was transitioned to hospice care and he died 23 months after the initial diagnosis.

Discussion

This report describes an elderly patient who went into complete remission with one dose of Venetoclax along with two doses of azacitidine. A review of current literature in PubMed does not report this phenomenon, although Complete Response (CR) after one cycle of treatment has been described [9]. While this patient developed mild hyperuricemia, he did not meet the criteria for laboratory tumor lysis syndrome. In addition, he developed a marked inflammatory response with fever and development of organizing pneumonia for which he was treated with steroids with improvement. This observation has not been previously described and whether this is an indicator of treatment response is unknown.

B-Cell Lymphoma-2 (BCL-2) and related antiapoptotic proteins inhibit mitochondrial outer membrane permeability *via* complex interactions with proapoptotic proteins. High expression of BCL-2 proteins is known to occur in tissues with high cell turnover such as bone marrow and plays an important role in the survival of AML blasts, thereby making this a promising therapeutic target. BAX is released upon inhibition of BCL-2, resulting in increased mitochondrial permeability and cell death [10,11]. The first generation BCL-2 inhibitor, Navitoclax exhibited activity in lymphoid malignancies, but co-inhibition of BCL-xL caused dose-limiting thrombocytopenia limiting its further development [12]. Venetoclax is a selective oral BCL-2 inhibitor that has been approved for the treatment of Chronic Lymphocytic Leukemia (CLL) and AML in combination with hypomethylating agents or low-dose cytarabine [8,13]. Studies have also demonstrated activity in other non-Hodgkin's lymphomas and multiple myeloma [14,15].

The efficacy of Venetoclax in AML has been demonstrated in multiple studies. A phase II study of Venetoclax monotherapy by Konopleva et al. demonstrated an objective response rate of 19% with 6% attaining CR and 13% attaining CR with incomplete recovery of counts (CRi). This study included 32 patients with AML; 94% who had received at least one prior treatment and 41% who had received at least 3 prior treatments [16]. Combining Venetoclax with hypomethylating agents may help overcome resistance by reducing levels of an antiapoptotic protein MCL-1 [17]. The study published by DiNardo et al. which included previously untreated patients who were 65 years or older and unable to receive standard induction chemotherapy and received Venetoclax at different doses along with azacitidine or decitabine demonstrated that 67% of patients achieved CR and CRi, with median overall survival of 17.5 months. The treatment was effective in patients with poor-risk cytogenetics and showed deeper responses with 29% of patients in CR and CRi attaining minimal residual disease below the level of 10^{-3} during treatment. Grade 3/4 adverse effects noted included cytopenia and pneumonia [8]. The phase III trial of Venetoclax with azacitidine versus azacitidine in treatment naïve patients with AML ineligible for standard induction therapy was published recently [VIALE-A trial]. The study showed a median overall survival of 14.7 months in the combination arm and 9.6 months in the control arm at a median follow-up of 20.5 months. CR rate was 36.7% versus 17.9% and CR with CRi was 66.4% versus 28.3% in the combination arm and control arm respectively [18].

Various biomarkers have been described as potential indicators of sensitivity and resistance to Venetoclax treatment. Several studies have reported a better response to Venetoclax in AML patients with Isocitrate Dehydrogenase (IDH) 1 and 2 mutations [16]. Mutant IDH1 and IDH2 proteins produce the metabolite (R)-2-hydroxyglutarate which inhibits the activity of cytochrome oxidase on the mitochondrial electron transport chain, which in turn lowers the mitochondrial threshold to trigger apoptosis with the use of BCL-2 inhibitors [19]. The VIALE-A trial included 25% of patients with IDH1 and IDH 2 mutations in the combination arm and 22% in the control arm. The analysis showed that the CR with CRi was 75.4% and 12-month overall survival was 66.8% in the combination arm in the subgroup with IDH 1 and 2 mutations [18]. Similarly, improved responses have been noted in SRSF2/ZRSR2 mutations [20]. BCL-2 family protein expression has also been correlated with clinical outcomes [16]. In another study, overexpression of HOXA and HOXB genes were identified in highly sensitive samples, and higher expression of beta 2-microglobulin was noted in resistant samples [21]. Certain studies have shown FLT3 mutations causing resistance to treatment, while certain others have not demonstrated this [8,20]. Further studies are required to confirm these findings. Our patient had an IDH1 mutation which could be the explanation for the noted response.

Combination therapy of Venetoclax with drugs with alternate mechanisms of action could be synergistic, reverse treatment resistance, and further improve treatment responses. Venetoclax in combination with the Cyclin-Dependent Kinase (CDK) 9 inhibitor, alvocidib has been shown to increase apoptotic mechanisms in AML cells [22]. PI3K inhibitors and MDM2 antagonists, idasanutlin have also been shown to potentiate cell death in preclinical models [23,24]. Combination treatment with the JAK inhibitor, ruxolitinib has also been shown to restore the sensitivity of Venetoclax to AML cells [25]. These need to be further explored in clinical studies.

Conclusions

The landscape of management of AML is rapidly evolving as newer targeted agents are being approved for treatment. Older patients who previously had high mortality due to the disease are now

eligible for treatment with these agents with an acceptable toxicity profile. As we gain more understanding and experience with these newer drugs, a subset of patients could potentially be candidates for treatment with modified regimes which involves less drug exposure while maintaining remission and preserving the quality of life in the elderly population.

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Author Affiliations

Top

[1]*Suny Upstate Medical University, Syracuse, New York, USA*

[2]*LSU Health Sciences Center, Shreveport, LA, USA*