Decitabine in Combination with Venetoclax in Six Elderly Patients with Acute Myeloid Leukemia (AML)

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Abstract

Background: High expression of the B-cell lymphoma 2 protein (BCL-2) contributes to chemotherapy resistance in AML[1]. Venetoclax is a selective small molecule inhibitor of BCL-2 with demonstrated efficacy and safety in chronic lymphocytic leukemia. Recently, DiNardo et al reported on the efficacy and tolerability of venetoclax in combination with hypomethylating agents (5-day decitabine or 7-day azacitadine) in elderly AML[2]. We report on six elderly patients with treatment-naïve AML treated with venetoclax in combination with 10-day decitabine**. Methods:** Six patients were treated with decitabine 20 mg/m² on days 1-10 of a 28-day cycle in combination with continuous venetoclax 200 mg once daily. All 6 patients were on daily fluconazole for fungal prophylaxis, a moderate CYP3A4 inhibitor. Decitabine was de-escalated to 20 mg/m² on days 1-5 of a 28-day cycle if a complete remission was achieved. **Results:** The median age is 71 years [range: 62-83 years]. Cytogenetic risk was poor in 3 patients, and intermediate in 3 patients. Two patients had secondary AML. All 6 patients achieved a complete remission. All patients had received at least four courses of therapy by the time of this report and all patients experienced myelosuppression managed with supportive therapy, including vigorous use of G-CSF. Sepsis occurred in four patients. There were no deaths. **Conclusions:** These results suggest that the combination of 10-day decitabine and venetoclax warrants further exploration as a potentially effective AML regimen with manageable toxicities.

Background

Elderly patients diagnosed with AML have poor outcomes due to high rates of induction death with standard intensive regimens and higher frequency of poor prognostic factors. Decitabine, an azanucleoside agent approved for treatment of myelodysplastic syndrome (MDS), has shown activity in elderly AML patients. The effective schedule in the elderly is 20 mg/m2 per day as a 1-hour intravenous infusion for ten consecutive days every 4 weeks[3]. Based on repots of venetoclax activity in combination with azanucleosides in elderly patients with AML[2], we combined venetoclax with 10-day decitabine to treat six patients consecutively and report on the outcomes herein.

Baseline Characteristics

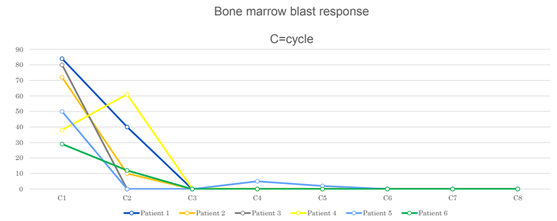
	Age	Sex	Presenting WBC count (X10³/µL)	De Novo or Secondary	Cytogenetics
Patient 1	82	F	2.8	De Novo	46, XX FLT3-ITD, IDH2, NPM1, NRAS, SRSF2
Patient 2	72	M	6.5	De Novo	46, XY DNMT3, NRAS, RUNX1, TET2, U2AF1, BCOR
Patient 3	77	M	325	De Novo	46, XY FLT3-ITD and NPM1
Patient 4		M	2.7	Secondary (t-AML*)	45X, -Y, -5q, -7q, -7, -16, -20, -17p TP53
Patient 5	72	M	1.2	De Novo	47, XY +mar[20] BCOR, DNMT3A, NRAS, RUNX1, STAG2, U2AF1, WT1
Patient 5	63	M	145	Secondary (CMML**)	46, XY ASXL1, RUNX1, STAG2, CEBPA, SRSF2

*treatment-related AML
**chronic myelomonocytic leukemia

Methods

The cohort consisted of 6 patients who were unfit for intensive induction chemotherapy based on age and/or comorbidities. They were treated with a combination of decitabine 20 mg/m² IV on days 1-10 of a 28-day cycle and venetoclax 200 mg orally daily on days 1-28. Venetoclax dosing was adjusted for concomitant fluconazole use. G-CSF was given daily on days 1-10 an as clinical course dictated subsequently. Treatment interruptions were also determined as the clinic course dictated.

Results



Relapse in patient 5 occurred after a 5.5-month delay in receiving cycle 3. Complete remission was achieved after resuming therapy

Relapse in patient 6 occurred after a 6-week delay in receiving cycle 3 and presented with proliferative disease and central nervous system involvement

Grade 3/4 toxicity	N (%)
Myelosuppressions	6/6 (100%)
Neutropenic fever	6/6 (100%)
Sepsis	5/6 (83%)
Bacteremia	4/6 (66%)
Pneumonia	3/6 (50%)
Diarrhea	3/6 (50%)
Perianal abscess	3/6 (50%)
Venous catheter infection	2/6 (33%)
Influenza	2/6 (33%)
Septic shock	1/6 (16%)
Urinary tract infection	1/6 (16%)
Proctitis	1/6 (16%)
Diverticulitis	1/6 (16%)
Orchitis	1/6 (16%)
Deep venous thrombosis	1/6 (16%)
Atrial fibrillation	1/6 (16%)
Supraventricular tachycardia	1/6 (16%)
Tumor lysis syndrome (TLS)	1/6 (16%)
Empyema	1/6 (16%)

This report describes 6 patients with intermediate and poor risk AML who achieved a complete remission after an average of 1.6 cycles of 10-day decitabine with venetoclax. Poor risk patients did not differ in their time to remission from the rest of the cohort. Further follow up is needed to determine duration of response and stratification according to their respective risk group. High-grade toxicities were common yet manageable and none were fatal. Toxicities resulted in treatment delays in all patients of an average of 102.1 days (range 65-186). Disease relapse occurred in 2 patients and was attributed to treatment interruptions due to toxicities, no patient relapsed while on therapy. Tumor lysis syndrome (TLS) is not a common finding with venetoclax in AML; patient 6 developed TLS prior to initiating venetoclax. Myelosuppression was a universal finding and managed with supportive blood product transfusions and the judicial use of G-CSF.

Summary

BCL-2 inhibition with venetoclax may enhance leukemic control in patients with AML compared to single-agent decitabine. Current literature is restricted to descriptions and early-stage trials. We await advanced prospective trials to evaluate this perceived potential for venetoclax in AML and to study the risk-adjusted benefit.

References

1.Campos L., Rouault J., 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

2.DiNardo C., Pratz K., et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitadine in elderly patients with previously untreated acute myeloid leukemia: a non-randomized , open-label, phase 1b study. Lancet Oncol 2018; 19:216-28

3.Blum W, Garzon R, et al. Clinical response and *miR-29b* predictive significance in older AML patients treated with a 10-day schedule of decitabine. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;107(16):7473-7478.