Venetoclax in Combination with Hypomethylating Agents Compared to Standard Chemotherapy in Relapsed/Refractory Acute Myeloid Leukemia

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Background: Recently, venetoclax with hypomethylating agents (HMA) was approved for treatment of newly diagnosed acute myeloid leukemia in elderly patients or patients with comorbidities that preclude the use of intensive chemotherapy. The place in therapy for less intensive regimens, such as venetoclax and hypomethylating agents, in relapsed/refractory acute myeloid leukemia (r/r AML) is under debate. Studies directly comparing outcomes and safety with standard chemotherapy regimens are lacking.

Objective: The objective of this study was to determine if treatment with venetoclax and HMA (VEN/HMA) therapy will exhibit similar or improved outcomes and a better toxicity profile compared to standard chemotherapy (SC) in r/r AML.

Methods: This was a single-center, retrospective chart review of adult patients at the Inova Fairfax Medical Campus treated with either VEN/HMA or SC for r/r AML. Patients were identified via electronic medical record and Web Intelligence report. The primary endpoint was overall response rate (ORR), defined as the combined rate of complete remission (CR), complete remission with incomplete hematological recovery (CRi), morphological leukemia-free state (MLFS), and partial recovery (PR) among all study subjects. Definitions of CR, CRi, MLFS, and PR are based on the 2017 European LeukemiaNet international panel on the diagnosis and management of AML. Response rate was assessed either through the provider's stated assessment of treatment response in the electronic health record or the investigator's assessment of lab values and markers of treatment response.

Secondary outcomes included overall survival, survival at 1 year from treatment initiation, relapse-free survival, duration of response, time to best response, induction mortality rate at 30 and 60 days, rates of stem cell transplantation, and induction safety. Toxicities were defined by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Preliminary Results: A total of 280 patients were screened, of which 24 patients were included in the VEN/HMA group and 34 patients in the SC group. Decitabine was the most commonly used hypomethylating agent compared to azacitidine (79.2% vs 20.8%). In terms of SC regimens, MEC (mitoxantrone, etoposide, cytarabine) was the most frequently used at 73.5% followed by ME (mitoxantrone, etoposide) at 14.7%, FLAG-IDA (fludarabine, cytarabine, granulocyte-colony stimulating factor, idarubicin) at 8.8%, and FLAG (fludarabine, cytarabine, granulocyte-colony stimulating factor) at 2.9 percent. Baseline characteristics, including age, number of prior therapies, grade $\geq$ 3 cytopenias at treatment initiation, ELN risk stratification, rates of de novo vs secondary AML, and rates of relapsed vs refractory AML were similar between groups.

Results of our primary outcome showed no statistically significant differences between VEN/HMA and SC treatment: ORR (50 % vs 44.1%), CR (25% vs 23.5%), CRi (4.2% vs 11.8%), MLFS (16.7% vs 5.9%), and PR (4.2% vs 2.9%). There was no difference in 1-year survival rates (33.3% vs 32.4%, p = 0.937), time to

best response (44 days vs 26 days, p =0.645), rates of disease relapse (50% vs 66.7%, p = 0.711), and rates of stem cell transplantation (20.8% vs 29.4%, p = 0.462) between VEN/HMA and SC treatment. Induction mortality, both at 30 days (4.2% vs 0%, p = 0.314) and 60 day (12.5% vs 2.9%, p = 0.297), was similar in both groups and overall low in this population.

Patients treated with VEN/HMA experienced lower rates of any grade diarrhea (37.5% vs 73.5%, p = 0.006), any grade mucositis (20.8% vs 58.5%, p = 0.007), and grade $\geq$ 3 anemia (79.2% vs 97.1%, p = 0.028). There was no difference in rates of any grade neutropenia, thrombocytopenia, nausea, vomiting, constipation, skin rash, transaminitis, or hyperbilirubinemia. In terms of hematologic recovery, patients in the VEN/HMA group experienced shorter durations of neutrophil nadir (19 days vs 25 days, p = 0.036) and faster platelet recovery (28.5 days vs 44 days, p = 0.013). Furthermore, rates of febrile neutropenia (37.5% vs 97.1%, p < 0.00001) and bacterial infections (20.8% vs 50%, p = 0.031) were lower with VEN/HMA treatment. There was also a non-statistically significant trend toward higher rates of fungal infections with SC treatment (25% vs 41.2%, p = 0.201). Of note, antifungal prophylaxis was used more frequently in the SC group (12.5% vs 91.2%, p < 0.0001), with fluconazole being the most frequently used antifungal agent.

Finally, patients treated with VEN/HMA completed induction as an outpatient in 58.3% of cases, compared to no patients in the SC arm (p < 0.0001). During inpatient induction, length of hospital stay was about three-fold higher with SC (13 days vs 34 days, p = 0.05).

Conclusion: Treatment with VEN/HMA and SC resulted in similar response rates in r/r AML patients, although a more favorable toxicity and infection profile was observed in patients treated with VEN/HMA.