Sequential Venetoclax and FLT3 Inhibitors in Combination with Hypomethylating Agents or Low-Dose Chemotherapy in Newly Diagnosed, Unfit, *FLT3*-mutant Acute Myeloid Leukemia Patients

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Introduction

- Targetable mutations such as FLT3, a receptor tyrosine kinase, are present in 30% of cases with acute myeloid leukemia (AML).
- Direct inhibitors of FLT3 are promising therapeutic agents such as midostaurin and gilteritinib.
- The use of FLT3 inhibitors as single agents remain to be limited with short-lived responses.
- For treatment-naïve AML patients with FLT3 mutation, the standard treatment entails induction with intensive chemotherapy in physically fit or younger patients and in combination with a FLT3 inhibitor.
- There is no approved targeted therapy option for treatment-naïve patients with AML harboring a FLT3 mutation ineligible for intensive therapy.

Objective

To assess the efficacy and feasibility of sequential administration of venetoclax, a selective inhibitor of Bcl-2, and midostaurin in addition to induction chemotherapy in unfit newly diagnosed FLT3-mutant AML patients.

Methods

- This is a case series reviewing the clinical data of four consecutive patients with FLT3-mutant AML, ineligible for standard induction chemotherapy at the time of diagnosis (had severe infection or had poor performance status), who received induction treatment consisting of low-dose chemotherapy or hypomethylating agents (HMA) with the sequential use of venetoclax for 10 days followed by midostaurin for 14 days, and treated at the American University of Beirut Medical Center.

Results

- Between November 2021 and February 2022, four patients were included in our study.
- The median age was 68 years (range 66-70).

	Patient 1	Patient 2	Patient 3	Patient 4
Age (yrs)	67	68	70	66
Gender	Male	Female	Male	Male
Past Medical History	HTN, DM	DM	CAD, HTN	MDS, RCC
Past Surgical History	None	Cholecystectomy	CABG	Partial nephrectomy
Clinical presentation	Fatigue, oral ulcers	Fever	Fever, unintentional weight loss, gingival hyperplasia	Anemia, thrombocytopenia
Pathology	AML (monocytic)	AML	AML (monocytic)	AML with myelodysplasia-related features
Molecular profile	NPM1, FLT3 TKD	NPM1, FLT3 ITD	NPM1, FLT3 ITD	FLT3 ITD
NGS testing	FLT3, IDH1,KIT	TET2	TET2	FLT3, KIT, SRSF2
Cytogenetics	47,XY,+8[2]/46,XY[24]	46,XX[4]	46,XY[20]	46,XY,del(7)(q31)[8]

Table 1. Baseline characteristics

- The median number of days for ANC and platelet count recovery was 40 days (range 27-59) and 34 days (24-not reached) respectively.
- The main toxicity reported was febrile neutropenia in 3 out of 4 patients.

	Patient 1	Patient 2	Patient 3	Patient 4
Induction treatment	Clad/LDAC/ Ven-Mido	Dec/Ven -Mido	Clad/LDAC/ Ven -Mido	Aza/Ven -Mido
Outcomes				
Day 21 evaluation	No blasts, NPM1 -, FLT3 -, 46,XY[8]	No blasts, NPM1 -, FLT3 +	No blasts, NPM1 -, FLT3 -	No blasts, FLT3 ITD +, Deletion 7
Day 28 evaluation	No blasts, MRD negative	No blasts, MRD negative	No blasts, MRD negative	No blasts, FLT3 ITD positive, Deletion 7
Time to ANC recovery (days)	27	41	34	59
Time to platelet count recovery (days)	24	48	29	NR
Toxicity during induction	Febrile neutropenia	Febrile neutropenia	Febrile neutropenia	None

Table 2. Induction treatment and outcomes

Discussion

- FLT3 mutations have been shown to be associated with lower response to venetoclax as a single agent and possibly in combination, in part due to upregulation of the MCL-1 protein, which is an anti-apoptotic protein of the BCL-2 family that prevents apoptosis by binding to the pro-apoptotic BCL-2 proteins. On the other hand, FLT3 and BCL-2 inhibition were shown to work in concert.
- The role of venetoclax and FLT3 inhibitors in combination with low-dose chemotherapy in AML patients who are unfit for high-intensity chemotherapy has been shown to positively affect survival in newly diagnosed AML patients.
- Preclinical data on the combination of Venetoclax and FLT3 inhibitors have showed promising results given the synergistic anti-leukemic effect these two drugs possess against FLT3-mutated AML.
- From our data, we can conclude that the use of sequential therapy is efficacious.
- Disease evaluation at day 21 and 28 showed no increase in blasts for all patients with count recovery after a median of 40 days for ANC and 34 days for platelets.
- Molecular and cytogenetic complete remission were reported in 3 out of 4 patients.
- Febrile neutropenia was the most commonly reported toxicity, which was limited. Patients received intravenous antibiotics as per protocol, and recovery occurred with no major morbidity nor mortality.
- After a median follow up of 150 days, all patients remain in remission and alive.
- 3 patients eventually underwent allogenic stem cell transplant and continue to be disease free and 1 patient completed consolidation therapy.

Conclusions

- The sequential use of venetoclax followed by midostaurin in combination with low dose chemotherapy or HMA for newly diagnosed AML, FLT3-mutant patients who are unfit for intensive chemotherapy seems to be a promising approach with acceptable toxicity profile.
- Further studies and randomized control trials are encouraged to better delineate the feasibility of this treatment approach in the aforementioned population. Future analyses in larger patient populations may further define the impact of the suggested sequential therapy.

Disclosures

- All authors have no conflict of interest.

Abbreviations: yrs: years, NGS: Next generation sequencing, HTN: hypertension, DM: diabetes mellitus, AML: acute myeloid leukemia, CAD: coronary artery disease, CABG: coronary artery bypass graft, RCC: renal cell carcinoma, MDS: myelodysplastic syndrome, Clad: Cladribine, Dec: decitabine, LDAC: low dose cytarabine, Ven: venetoclax, Mido: midostaurin, + positive, - negative, MRD: minimal residual disease, ANC: absolute neutrophil count

Bibliography:

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