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Title: SELINEXOR IN COMBINATION WITH VENETOCLAX AND HYPOMETHYLATING AGENTS FOR ACUTE MYELOID LEUKEMIA PATIENTS WITH SEVERE CO-MORBIDITIES

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Background:

Acute myeloid leukemia（AML）is primarily a disease of the elderly with a median age of 67 years, and usually manifests at onset with complicated comorbidities or severe infections. Such patients cannot tolerate intensive chemotherapy, even the standard dosing of azacytidine plus venetoclax, and are usually excluded from clinical trials. Selinexor has proved its tolerability and clinical activity in AML in a few phase 1/2 trials.

Aims:

To report the efficacy and safety of eight cases of AML patients ineligible for intensive therapy who were treated with triple regimen including selinexor, venetoclax and hypomethylating agents in our center.

Methods:

Data of eight patients with AML who received a triple regimen of selinexor, venetoclax and hypomethylating agents are retrospectively collected from December, 2021. Selinexor was given at 60mg/day at day 3, 10, 17 for 28 days a cycle. The dose of venetoclax was 100mg day 1, 200mg day 2, and 400mg from day 3 to day 14, the dosing duration adjusted by the physicians from 5 days to 14 days. Hypomethylating agents, either decitabine (0.1-0.2mg/kg) or azacytidine (75mg/m2) were administered with intermittent dosing schedule day 1-3, day 8-9(10), and/or day 15-16(17). The triple regimen was approved by the ethics committees of Shanghai Tongren Hospital, and all patients provided written informed consent.

Results:

The median age of 8 patients was 67 years with a range of 51-76 years. One patient previously received one cycle of idarubicin and cytarabine (IA) without response and other 7 patients were newly diagnosed AML patients. Five patients had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 4 with pulmonary infections requiring intravenous intervention. Among them, co-morbidities also included diabetes with ketoacidosis, multiple subacute cerebral infarctions, COVID-19 pneumonia and advanced colon cancer. Seven patients were classified as adverse-risk group and one classified into intermediate group based on the 2022 ELN risk stratification. The complete remission plus complete remission with incomplete hematologic recovery rate (CR+CRi) was 100% (8/8). The median follow-up time was 5 months (range: 1-18), with no responders experiencing relapses and all 8 patients alive. Patient 5 didn't respond after cycle 1, and avapritinib was added on in cycle 2 because of the c-Kit mutation detected, and then achieved CRi. Patient 1 achieved CR after two cycles of the triple regimen and one cycle of high dose cytarabine consolidation and then underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT). Two patients had myelosuppression grades 3/4, and two patients developed left ventricular failure and acute pulmonary embolism, respectively, which were considered due to their underlying conditions and recovered from supportive care. The common non-hematological adverse events were mainly grade 1 or 2 including fatigue, nausea, and vomiting.

Summary/Conclusion:

These results imply that the triple regimen of selinexor, venetoclax and hypomethylating agents are potentially highly effective in AML patients, even for those with serious infections or other comorbidities. Based on this preliminary result, we designed a prospective study to further evaluate the efficacy and safety of the triple regimen of selinexor, venetoclax, and azacytidine (SAV regimen) for newly diagnosed patients with AML ineligible for

intensive therapy (NCT05736965).

Table1. Patients' clinical characteristics and treatment outcome

No.	Age	FAB subtype	ECOG	Comorbidities	Bone marrow blast count	ELN 2022	Regimen	Best of response	Remission duration/months
1	56	AML M5	4	Pulmonary infection	94%	Adverse	S+V+Dec	CR	18+ (Proceeded to allo-HSCT after CR)
2	61	AML M4	1	None	37.5%	Intermediate	SAV	CR	6+
3	69	AML M2a	4	Pulmonary infection, Diabetes with ketoacidosis	43%	Adverse	SAV	CRi	8+
4	70	AML M5b	1	Hypertension, Chronic bronchitis	34%	Adverse	SAV	CR	4+
5	51	AML M2	4	Pulmonary infection	57%	Adverse	SAV/SAV+avapritinib	CRi	2.5+
6	76	AML M4	4	Pulmonary infection, Multiple subacute cerebral infarctions, COVID-19 pneumonia	55.5%	Adverse	SAV	CRi	2+
7	65	AML M5b	2	Pulmonary infection	25.5%	Adverse	SAV	CRi	2+
8	74	AML	4	Pulmonary infection Advanced colon cancer	20%	Adverse	SAV	CR	1+

Abbreviations: S+V+Dec: Selinexor+venetoclax+decitabine

Keywords: Acute myeloid leukemia, Venetoclax, Hypomethylating agents