Selinexor maintenance is feasible and tolerable after allogeneic stem cell transplant (allo-SCT) for patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)

Hongtao Liu, MD, PhD; Andrew S. Artz, MD; Richard A. Larson, MD; Satyajit Kosuri, MD; Wendy Stock, MD; Michael Bishop, MD

Department of Medicine, Section of Hematology/Oncology, University of Chicago Medical Center, Chicago, IL

Abstract

Background: Selinexor, an oral exportin 1 (XPO1) inhibitor, has demonstrated anti-leukemic effects as a single agent in relapsed/refractory AML. We hypothesized that selinexor could be used as maintenance therapy after allo-SCT to prevent disease relapse in patients with AML and MDS.

Methods: This phase I trial tests selinexor as a maintenance therapy in patients with AML/MDS undergoing allo-SCT (NCT02485535). The primary endpoint was to determine the maximum tolerated dose (MTD) of selinexor after allo-SCT. Patients were enrolled approximately day 60 to day 100 post allo-SCT if there was no GVHD or disease relapse. Once weekly oral selinexor started approximately 100 days post allo-SCT, and continued for 12 months if tolerated, and there was no relapse of disease. Dose limiting toxicity (DLT) was defined as any grade 3 or higher treatment-related adverse event (AE) that occurred within the first treatment cycle (28 days).

Results: From January 2016 to March 2017, nine patients were enrolled including seven with AML and two with MDS. Selinexor dose levels were 60mg weekly (n=6) and 80mg weekly (n=3). Per stem cell transplant disease risk index (DRI), three patients had high risk and six had intermediate risk. Six patients with AML entered allo-SCT in CR (five CR1, one CR2) and one patient had refractory AML. Two MDS patients had active disease at the time of transplant. Four patients had matched related donors (MRD), two had matched unrelated donors (MUD), and three had haplo/cord SCT. One patient had myeloablative conditioning, and eight had RIC. The median time from allo-SCT to first dose of selinexor was 97 days (range: 66-102). One of the first three patients treated at 60mg weekly developed grade 3 nausea, thus three more patients were enrolled to the 60mg weekly dose level. After no additional DLTs at 60mg weekly, patients were enrolled to 80mg weekly dose level. While there was no DLT during the first cycle treatment at 80mg weekly, the dose of selinexor was decreased to 60mg weekly at the beginning of cycle 2 due to decreased chimerism in one patient and in one in cycle 3 due to neutropenia; one patient stopped treatment in the middle of cycle 2 due to leg cramping. The RP2D of selinexor post allo-SCT was determined to be 60mg weekly. The most common AEs were fatigue (67%), anorexia (56%), nausea (56%), vomiting (33%) and diarrhea (22%) which were grades 1-2 with the exception of one case of grade 3 nausea. These AEs were manageable with adequate supportive care, including ondansetron, dexamethasone, megestrol and short hold of drug. Two patients finished 12 cycles of treatment without major complications. One patient developed grade 1 skin GVHD during tapering immunosuppression not related to selinexor, and 2 patients developed skin and/or liver GVHD after donor lymphocyte infusion (DLI) for low chimerism, which was not related to selinexor. With median follow-up of 359 (219-639) days from transplant, two patients had disease relapse after 2 and 4 cycles of treatment, of which one patient died from disease progression. Three patients are still on treatment, three patients are off study due to tolerability (Neutropenia=1, fatigue=1, and cramping in leg=1), and one patient is off study due to liver GVHD after donor lymphocyte infusion (DLI). The median remission duration from the start of selinexor treatment was 199 (59-542) days. Correlative studies for MRD monitoring and immune reconstitution are on-going.

Conclusions: Selinexor maintenance after allo-SCT is feasible and tolerable without increased risk of GVHD. The recommended phase II dose of selinexor maintenance post allo-SCT is 60mg weekly. Additional patients are being enrolled to the expansion cohort at the dose of 60mg weekly for better understanding of the toxicities and efficacy.

Background

- Relapse after allogeneic stem cell transplantation remains as one of most common treatment failures for patients with AML/MDS.
- Maintenance therapies post-SCT have demonstrated efficacy in patients with MM and lymphoma.
- Targeted therapies for certain mutations have been attempted post-SCT, such as sorefenib for patients with FLT3 mutated AML, and TKI for patients with Ph+ ALL.
- Selinexor, an oral exportin 1 (XPO1) inhibitor, has demonstrated anti-leukemic effects as a single agent in relapsed/refractory AML.
- We hypothesized that selinexor could be used as maintenance therapy after allo-SCT to prevent disease relapse in patients with AML and MDS

Methods

- This phase I trial tests selinexor as a maintenance therapy in patients with AML/MDS after allo-SCT (NCT02485535).
- The primary endpoint was to determine the maximum tolerated dose (MTD) of selinexor after allo-SCT.
- Patients were enrolled approximately day 60-100 post allo-SCT if there was no GVHD or disease relapse. Once weekly oral selinexor started approximately100 days post allo-SCT, and continued for 12 q28 days cycles if tolerated, and there was no relapse of disease.
- Dose limiting toxicity (DLT) was defined as any grade 3 or higher treatment-related adverse event (AE) that occurred within the first treatment cycle (28 days).

Clinical Trial Design

Dose Level	Selinexor
- 1	40 mg weekly (160 mg per cycle)
1	60 mg weekly (240 mg per cycle)
2	80 mg weekly (320 mg per cycle)

Patient Characteristics and AEs

Table 1: Characteristics of the 9 patients in the dose escalation cohort

Characteristic	No
Total patients	9
Median Age (range)	58 (44-73)
Diagnosis	
AML	7
MDS	2
Donor status	
MRD	4
MUD	2
Haplo-cord	3
Conditioning regimen	
Myeloablative (Flu-Bu/TBI based)	1
RIC (Flu-mel)	8
Disease status prior to SCT	
CR1/CR2	5/1
R/R/PIF	2/1
Disease Risk Index (DRI)	
Intermediate	6
High	3

Table 2: Adverse event profiles of selinexor maintenance. One patient in the 60mg cohort had Grade 3 nausea (DLT), thus three more patients were enrolled into 60mg cohort without DLT, three patients were started on 80mg cohort without DLT, but all had dose reduction after cycle 1. MTD was determined to be 60mg weekly.

Adverse Events	Total, n (%)	Grade 1&2	Grade 3	Grade 4
Related to Selinexor				
Fatigue	6 (67%)	6 (67%)		
Anorexia	5 (56%)	5 (56%)		
Nausea	5 (56%)	4 (45%)	1 (11%)	
Vomiting	3 (33%)	3 (33%)		
Diarrhea	2 (22%)	2 (22%)		
Taste changes	1 (11%)	1 (11%)		
Dry mouth	1 (11%)	1 (11%)		
Numbness of finger	1 (11%)	1 (11%)		
Hallucination	1 (11%)	1 (11%)		
Muscle pain	1 (11%)	1 (11%)		
Thrombocytopenia	1 (11%)	1 (11%)		
Vision abnormality	1 (11%)	1 (11%)		
Neutropenia	1 (11%)	1 (11%)		
Hyperkalemia	1 (11%)	1 (11%)		
CMV reactivation	1 (11%)	1 (11%)		
AEs Unrelated to Selinexor				
Constipation	1 (11%)	1 (11%)		
Throat infection	1 (11%)	1 (11%)		
Bacteremia	1 (11%)			1 (11%)
Elevation of LFTs	1 (11%)			1 (11%)
Hip fracture	1 (11%)			1 (11%)
Dizziness	1 (11%)	1 (11%)		
Polyuria	1 (11%)	1 (11%)		

Chimerism and immune re-constitution

	Donor type	Day 30	Day 100	Day 128 (after one cycle selinexor)	Day 180	Day 365
BM Chimerism (unfractionated)	Haplo-cord	95	100	95		100
	MUD	100	95	100	95	95
BM chimerism (CD3 population)	Haplo-cord	95	95	73		90
	MUD	95	92	93	74	95
Absolute CD3 counts	Haplo-cord	0.8	846.16			170.28
	MUD	8.59	15.96		103.48	91.32
Absolute CD19 counts	Haplo-cord	2.13	19.13			611.06
	MUD	0.46	66.30		125.19	71.23
IgG level	Haplo-cord	363	335		582	737
	MUD	637	702		666	1016

Table 3: Chimerism and immune re-constitution on selinexor maintenance. Two patients recently finished selinexor maintenance without GVHD or disease relapse. Chimerism and immune re-constitution data are listed here. Both patients had mild decrease of donor chimerism especially in CD3 population, but rebounded later.

Transplant outcomes

Table 4: Engraftment and transplant outcomes of the patients on selinexor maintenance

Characteristic	No
Dose level (60/80mg weekly)	6/3
Time form SCT to start of Selinexor	97 days (66-102)
Median Neutrophil engraftment	9 days (8-13)
Median platelet engraftment	15 days (13-37)

Characteristic	No
Time form SCT to start of Selinexor	97 days (66-102)
Days on selinexor treatment	98 days (37-NR-currently at 354 days)
Reasons off selinexor	
Disease relapse	2 (after 59 and 91 days on selinexor)
AEs	3
GVHD after DLI	2
Completed 12 cycle maintenance	2
Median PFS from SCT	359 days (125-NR-currently at 639 days)
Median OS from SCT	359 days (219-NR-currently at 639 days)
GVHD	
Grade I	1
GVHD after DLI	
Grade I-III	2

Conclusions

- Selinexor maintenance after allo-SCT is feasible and tolerable without increased risk of GVHD.
- The recommended phase II dose of selinexor maintenance post allo-SCT is 60mg weekly.
- Additional 20 patients are being enrolled to the expansion cohort at the dose of 60mg weekly for better understanding of the toxicities and efficacy. Three patients were already enrolled, it will take another 18 months to finish the full enrollment.

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Disclosure statement

Dr. Liu has research support from Karyopharm. There is no other relevant conflict of interest related to this study.