Lintuzumab-Ac225 in Combination with CLAG-M Chemotherapy in Relapsed/Refractory AML: Interim Results of a Phase I Study.

Sameem Abedin, GS Guru Murthy, Laura C. Michaelis, Mehdi Hamadani, Lyndsey Runaas, Karen Carlson, Alexandra Harrington, and Ehab Atallah

Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee WI

BACKGROUND

- In a recent series of MCW & UW patients with relapsed/refractory AML (RR-AML) with similar clinical characteristics, CLAG-M yielded a higher overall complete remission rate (55%) than MEC (44%) or CLAG (40%)[1]
- Lintuzumab-Ac225 is a radioimmunoconjugate composed of actinium-225, an alpha-particle emitter, linked to the humanized anti-CD33 monoclonal antibody Lintuzumab
- Previous clinical studies with Lintuzumab-Ac225 have demonstrated potent single-agent anti-AML activity[2]
- On this basis, we hypothesized that low dose Lintuzumab-Ac225 administered after CLAG-M would eradicate residual chemo-insensitive leukemia and improve remission rates

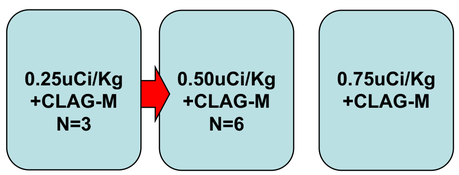
METHODS

- This is an ongoing, investigator-initiated, Phase I study to determine the safety and tolerability of Lintuzumab-Ac225 added to CLAG-M chemotherapy
- Medically fit patients with R/R AML, aged 18 years or older, with adequate organ function, were eligible for screening
- On screening, we required that >25% of leukemic blasts express the CD33 antigen by flow cytometry

- Eligible patients received CLAG-M re-induction, consisting of G-CSF 300mcg/d, given D1-6, cladribine 5mg/m2, given D2-6, cytarabine 2g/m2, given D2-6, and mitoxantrone 10mg/m2, given D2-4
- Upon completion of CLAG-M, Lintuzumab-Ac225 was administered as a single dose on either D7,8 or 9
- Cohort 1 received a Lintuzumab-Ac225 dose of 0.25uCi/kg
- Cohort 2 received a Lintuzumab-Ac225 dose of 0.50uCi/kg
- *Cohort 3, if opened, will receive a Lituzumab-Ac225 dose of 0.75uCi/kg*
- Only one induction course was administered, and subsequent treatment was up to physician discretion

RESULTS

Lintuzumab-Ac225 dose escalation



Patient Characteristics

Demographics		Prior CLAG-M Data (n=74)	Cohort 1: 0.25 uCi/kg (n=3)	Cohort 2: 0.5 uCi/kg (n=6)
Age, median (range)		60(23-77)	55 (50-69)	62 (47-73)
AML Cytogenetics n%	Favorable	5 (7)	0	0
	Intermediate	45 (61)	1 (33)	3 (50)
	Poor	24 (32)	3 (67)	3 (50)
Number of prior therapies n (%)	1	22 (30)	1 (33)	3 (50)
	2	47 (63.5)	1 (33)	0
	3 or more	5 (7)	1 (33)	3 (50)
Prior allogeneic HCT, n(%)		9 (12%)	1(33)	3(50)

Non-Hematologic Adverse Events and Hematologic DLTs

Grade 3-4 AEs		Cohort 1: 0.25uCi/kg (n =3)	Cohort 2: 0.50uCi/kg (n=6)
Hypophosphatemia	Grade 3	1(33)	
Hyponatremia	Grade 3	1(33)	
QT Prolongation	Grade 3		1(17)
Tumor lysis syndrome	Grade 3		1(17)
Febrile neutropenia	Grade 3	2(66)	2(33)
ANC<500 at 42 days	Grade 4		2 (33)

Time to count recovery among responders

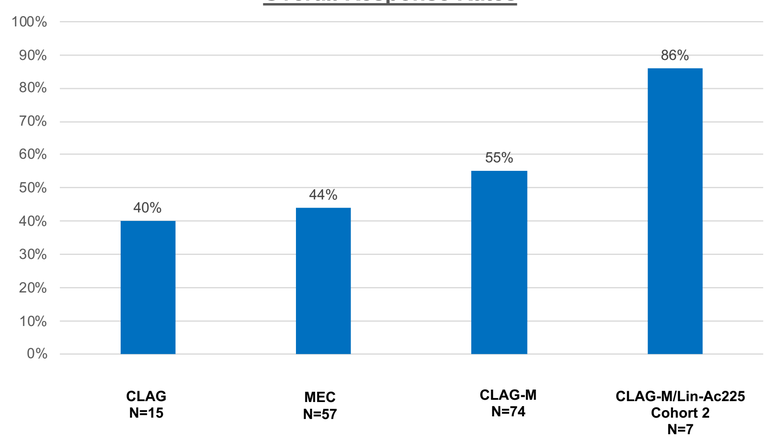
Responding Patients	Time to ANC > 1000	Time to Platelets > 50,000
Cohort 1, patient 1	27 days	35 days
Cohort 2, patient 1	37 days	n/a (initiated next therapy)[1]
Cohort 2, patient 2	58 days[4]	n/a (initiated next therapy)[2]
Cohort 2, patient 3	30 days	39 days
Cohort 2, patient 4	25 days	25 days
Cohort 2, patient 5	n/a (CD34+ boost D+43)[3,4]	n/a (CD34+ boost D+43)[3]
Cohort 2, patient 6	33 days	33 days

1. Initiated planned therapy upon achievement of platelet transfusion independence
2. Admitted for allogeneic HCT, achieved platelet transfusion independence after HCT
3. CD34+ select boost on D+43 given delayed count recovery, both ANC and platelets recovered
4. DLT due to ANC < 500 at Day 42

Treatment Response

Response, n(%)	Previous CLAG-M Data[1] (n=74)	Cohort 1: 0.25 uCi/kg (n=3)	Cohort 2: 0.5 uCi/kg (n=7)
CR+CRi	41(55)	1 (33)	6 (86)
Subsequent HCT	37 (50)	1(33)	2 (33)

Overall Response Rates



CONCLUSIONS

- The addition of Lintuzumab-Ac225 to CLAG-M appears to have a clinically acceptable safety profile.
- With dose escalation, a trend of increased myelosuppression is appreciated, but with highly encouraging efficacy results
- 86% remission rate in 2nd cohort is substantially higher than the remission rate in our prior series of similar patients treated with CLAG-M, MEC, or CLAG.

FUTURE DIRECTIONS

- To further characterize myelosuppression and efficacy, a protocol amendment was made to redefine DLT as Gr 4 neutropenia < 60 days, and additional patients are enrolling to Cohort 2.
- The encouraging results to date warrant a Phase II study, which could be a pivotal study, to further evaluate the efficacy of this promising combination.

References

1. Mushtaz et al, ASH 2018 poster 2605
2. E Atallah et al. JMIR 2019: 50(1); S37

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