API-01

A Phase 2 Study of Actinium-225 (^{225}Ac)-Lintuzumab in Older Patients with Previously Untreated Acute Myeloid Leukemia (AML) Unfit for Intensive Chemotherapy

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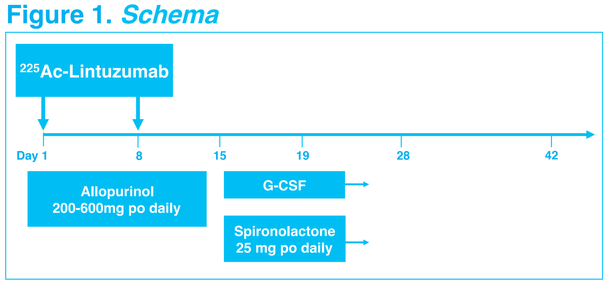
Background

- Older patients with AML unfit for induction chemotherapy have high early death rates and limited overall survival (OS), which vary depending on age, prior antecedent hematologic disorder, comorbidities, and ECOG performance status (PS) (Haematologica 2012;97:1916).
- ^{225}Ac-lintuzumab (Actimab-A) is a radioimmunoconjugate with a 3-day biologic half-life composed of ^{225}Ac linked to a humanized anti-CD33 monoclonal antibody.
- A Phase 1 trial of fractionated-dose ^{225}Ac-lintuzumab with low-dose cytarabine in older patients with untreated AML showed responses at 1.0, 1.5, and 2.0 µCi/kg/fraction.
- 2.0 µCi/kg/fraction was chosen as the Phase 2 therapeutic dose to limit myelosuppression.
- Responding patients had peripheral blasts of <200/µL which presumably leads to more effective drug delivery to bone marrow (ASH, 2016, Abstract 4050).
- A CD33 splicing polymorphism predicted response to another anti-CD33 directed therapy, gemtuzumab ozogamicin (GO). CT and TT polymorphisms provided no additional benefit from GO over chemotherapy alone, whereas a CC polymorphism showed benefit (JCO 2017;35:2674).

API-01 Study Design

Figure 1. ***Schema***



- Patients ≥ 60 years with untreated AML and ECOG performance status (PS) 0-3
- Patients 60-74 years of age were required to have significant cardiac, pulmonary, renal or hepatic impairment.
- Any patients ≥ 75 years of age was eligible.
- Patients with antecedent hematologic disorders (AHDs) were eligible, including those with prior AHD therapy.
- Expression of CD33 on > 25% of blasts was required.
- Patients were required to have a peripheral blast count <200/µL within 7-10 days of the first dose.
- Pre-treatment with Hydroxyurea was allowed to lower peripheral blast counts if necessary.
- ^{225}Ac-lintuzumab 2 µCi/kg was administered on Days 1 and 8.
- Granulocyte colony-stimulating factor (G-CSF) and spironolactone (nephrotoxicity prevention) was administered 10 days after second dose.

Results

Table 1. ***Patient Characteristics***

Characteristic	(N=13)	%
Median age (range), years	74 (65-82)	N/A
Male	10	77
ECOG Performance Status (PS)		
0 - 1	8	61
2	3	23
3	2	15
Antecedent hematologic disorder (AHD) (n=9)		
Myelodysplastic Syndrome (MDS)	5	38
Atypical Chronic Myeloid Leukemia (Atyp CML)	1	8
Chronic Myelomonocytic Leukemia (CMML)	2	15
Therapy-related AML (tAML)	1	8
Prior therapy for AHD		
Hypomethylating agent (HMA)	7	53
Allogeneic Hematopoietic Cell Transplantation	1	8
Immunomodulatory monoclonal antibody	1	8
Chemotherapy	1	8
Cytogenetics (n=6) 7 patients had missing data		
Intermediate-risk	1	8
High-risk	3	23
CD33 single nucleotide polymorphisms (SNP) (n=9)		
CT	6	46
CC	3	23

Among the responders, 2 patients had adverse cytogenetics including one who had t-AML. Two responders had ECOG Gr 3 at baseline, including the patient whose platelet count rose to 82K/uL prior to consolidation therapy. (See Table 2)

Table 2. ***Patient Characteristics and Response***

Patient ID	AHD	Prior therapy for AHD	PS	CD33 SNP	OR
1	MDS	Hypomethylating agent	0	ND	CRp
2	MDS	Lenalidomide, Ipilimumab, Hypomethylating agent	1	ND	CRi
3	MDS	Hypomethylating agent	0	CT	TF
4	MDS	Hypomethylating agent	2	CT	TF
5	Atyp CML	Hypomethylating agent	1	ND CT	TF
6	None	None	1	ND	CRi
7	MDS	Hypomethylating agent	2		Unk
8	None	None	3	CT	CRp
9	tAML	None	3	CC	CRi
10	None	None	0	CC	CRp
11	CMML	None	0	CT	CRi
12	CMML	Hypomethylating agent	0	CT	CRi
13	None	None	1	CC	CRi

Abbreviations: OR, Overall Response; ND, not done; CRp, CR with incomplete platelet recovery; CRi, CR with incomplete blood count recovery; TF, treatment failure; Unk, unknown.

Myelosuppression

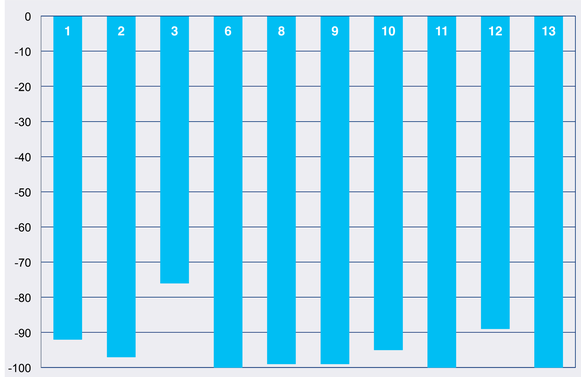
- Grade 4 myelosuppression was seen after treatment in all evaluable patients, although in many cases it was also present or was induced by hydroxyurea prior to treatment.
- At baseline, 6 patients had absolute neutrophil count (ANC) ≥ 500/µL; 2 had ANC ≥ 1000/µL, and 1 had platelets > 50,000/µL. The median baseline bone marrow blast percentage was 26% (range, 20-88%).
- The 3 patients with CRp had neutrophil recovery to 1000/uL at Days 60, 36, and 40.
- Four of the patients with CRi had not reached ANC ≥ 500/µL when they expired on Days 56 – 65 and one patient at Day 102 had continuing CRi. One patient with CRi received an allogeneic HCT at Day 122.
- The 30-day mortality rate was 23% (disease progression, acute chronic respiratory failure, and post-traumatic intracranial hemorrhage).

Table 3. ***Treatment-Emergent Adverse Events***

Related/Possibly Related Non-Hematologic Adverse Events Grade 3/4/5* * Veno-occlusive disease of any grade did not occur.	N = 13
Epistaxis	1
Fatigue	1
Febrile Neutropenia	1
Pneumonia	2
Pneumonia Fungal	1
Sepsis	1
Septic Shock	2

Figure 2. ***Percent Bone Marrow Blast Decrease***

Median, 98% decrease



*10 patients of the 13 had evaluable bone marrow aspiration after second dose

Case Study

- Patient 8 is a 74 year-old female patient without prior MDS, ECOG performance status (PS) 3 (See Table 2).
- Baseline marrow blasts were 88%.
- Day 96 bone marrow exam showed 1% AML blasts, a 99% decrease (See Figure 2).
- On Day 36, ANC was > 500/µL and by Day 39, ANC was > 1000/µL.
- Over the next several months, her platelet count rose to 82,000/µL before consolidation therapy with GO was begun.
- The patient continues to be in remission >180 days after the start of ^{225}Ac-lintuzumab.

Table 4. ***Objective Responses at 2 µCi/kg/fraction***

Response	(N=13)
CR with incomplete platelet recovery (CRp)	3 (23%)
CR with incomplete blood count recovery (CRi)	6 (46%)
Overall response rate (ORR)	9 (69%)

The primary endpoint was response rate, with a target response rate of 35%.

Conclusions

- ^{225}Ac-lintuzumab at a dose of 2.0 µCi/kg/fraction on Days 1 and 8 administered to an older population of AML patients unfit for standard chemotherapy is associated with a high overall response rate of 69%.
  - To improve biodistribution, hydroxyurea was used to lower peripheral blast counts before treatment with ^{225}Ac-lintuzumab.
  - Results are consistent with the Phase 1 finding that responses occurred in patients with < 200 peripheral blasts/µL.
- Patient responses occurred irrespective of splicing polymorphism status (CT vs. CC genotype) and of cytogenetic risk category.
- Doses of 2.0 µCi/kg/fraction were associated with a longer duration of myelosuppression than desirable in this patient population.
  - Doses of 1.5 µCi/kg/fraction with low-dose cytarabine were associated with a 67% response rate in a Phase 1 study in older untreated AML patients.
  - Therefore, the therapeutic dose was reduced to 1.5 µCi/kg on Days 1 and 8 in the ongoing Phase 2 trial.

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