

Phase I Trial of Targeted Alpha-Particle Therapy with Actinium-225 (²²⁵Ac)-Lintuzumab and Low-Dose Cytarabine (LDAC) in Patients Age 60 or Older with Untreated Acute Myeloid Leukemia (AML)

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Blood (2016) 128 (22) : 4050.

<http://doi.org/10.1182/blood.V128.22.4050.4050>

Abstract

Background: ²²⁵Ac-lintuzumab is a radioimmunoconjugate composed of ²²⁵Ac (t_{1/2}=10 days), which emits 4 α-particles, linked to a humanized anti-CD33 monoclonal antibody. Short-ranged (50-80 μm), high-energy (~100 keV/μm) α particle-emitting isotopes such as ²²⁵Ac may result in more specific tumor cell kill and less damage to normal tissues than β-emitters. An initial phase I trial in 20 patients with relapsed/refractory AML showed that a single infusion of ²²⁵Ac-lintuzumab is safe at doses ≤ 3 μCi/kg and has anti-leukemic activity (Jurcic *et al.* ASH, 2011). We conducted a multicenter, phase I dose-escalation trial to

determine the maximum tolerated dose (MTD), toxicity, and biological activity of fractionated-dose ^{225}Ac -lintuzumab in combination with LDAC.

Patients and Methods: Patients ≥ 60 years with untreated AML not candidates for standard induction therapy (*e.g.*, antecedent hematologic disorder, poor-risk cytogenetic or molecular features, and significant comorbidities) were eligible. Patients received LDAC 20 mg twice a day for 10 days every 4-6 weeks for up to 12 cycles. During Cycle 1, 2 fractions of ^{225}Ac -lintuzumab were given 1 week apart, beginning 4-7 days following completion of LDAC. To prevent radiation-induced nephrotoxicity, patients were given furosemide while receiving ^{225}Ac -lintuzumab then spironolactone for 1 year afterward. Four dose levels of ^{225}Ac -lintuzumab were studied using a 3+3 design. Dose escalation proceeded if $< 33\%$ of patients in a cohort experienced dose-limiting toxicity (DLT).

Results: Eighteen patients (median age, 77 years; range, 68-87 years) completed therapy. Twelve (67%) had prior myelodysplastic syndrome (MDS), for which 10 (83%) received therapy with hypomethylating agents ($n=9$) or allogeneic hematopoietic cell transplantation ($n=1$). One patient (6%) had chronic myeloid leukemia in molecular remission prior to developing AML. Eleven patients (61%) had intermediate-risk and 7 (39%) had poor-risk disease by NCCN criteria. Median CD33 expression was 81% (range, 30-100%). ^{225}Ac -lintuzumab was given at 0.5 ($n=3$), 1 ($n=6$), 1.5 ($n=3$), or 2 ($n=6$) $\mu\text{Ci/kg/fraction}$. Up to 4 cycles of LDAC were administered. Two patients experienced DLT (grade 4 thrombocytopenia with marrow aplasia for > 6 weeks following therapy), one each in the 1 and 2 $\mu\text{Ci/kg/fraction}$ cohorts. Although the MTD was not reached, 2 $\mu\text{Ci/kg/fraction}$ was chosen as the phase II dose to limit prolonged myelosuppression. Hematologic toxicities included grade 4 neutropenia ($n=5$) and thrombocytopenia ($n=9$). Grade 3/4 non-hematologic toxicities included febrile neutropenia ($n=6$), pneumonia ($n=5$), other infections ($n=3$), atrial fibrillation/syncope ($n=1$), transient creatinine increase ($n=1$), generalized fatigue ($n=1$), hypokalemia ($n=1$), mucositis ($n=1$), and rectal hemorrhage ($n=1$). Thirty- and 60-day mortality rates were 0% and 17%, respectively. Eleven of 14 patients (79%) evaluated after Cycle 1 had bone marrow blast reductions (mean reduction, 66%; range, 19-100%). Objective responses (2 CR, 1 CRp, 2 CRi) were seen in 5 of the 18 patients (28%), but only at doses $\geq 1 \mu\text{Ci/kg/fraction}$ (Table 1). One of the responders received 15 cycles of azacitidine for prior MDS. All responses occurred after 1 cycle of therapy, in contrast to historical data with LDAC alone, where the median time to response was 3 cycles. Median progression-free survival (PFS) for all patients was 2.7 months (range, 1.0-31.8+ months). Median overall survival (OS) was 5.6 months (range, 1.6-32+ months). Median response duration was 5.6 months (range, 4.9-32+ months). Peripheral blood blast counts were a strong predictor of response. Among 38 patients treated in the current and initial phase I trials, responses were seen in 8 of 19 patients (42%) with blast counts $< 200/\mu\text{L}$, compared with 0 of 17 patients with blast counts $\geq 200/\mu\text{L}$ ($P=0.002$).

This difference is likely due to decreased marrow targeting in patients with higher circulating blast counts when the subsaturating antibody doses used in this trial are given.

Conclusions: Fractionated-dose ^{225}Ac -lintuzumab can be safely combined with LDAC and induce remission in older patients with untreated AML. A phase II trial of ^{225}Ac -lintuzumab monotherapy at 2 $\mu\text{Ci/kg}$ /fraction using hydroxyurea, if needed, to lower peripheral blast counts prior to administration will be undertaken to determine response rate, PFS, and OS in this patient population.

Table 1. Objective Responses

Response	Dose Level ($\mu\text{Ci/kg}$ /fraction)				Total (n=18)
	0.5 (n=3)	1 (n=6)	1.5 (n=3)	2 (n=6)	
CR	0	1 (17%)	1 (33%)	0	2 (11%)
CRp	0	0	0	1 (17%)	1 (6%)
CRi	0	0	1 (33%)	1 (17%)	2 (11%)
Overall Response	0	1 (17%)	2 (67%)	2 (33%)	5 (28%)

Abbreviations: CR, complete remission; CRp, CR with incomplete platelet recovery; CRi, CR with incomplete count recovery.

Disclosures

Jurcic: *Forma Therapeutics:* Research Funding; *Seattle Genetics:* Research Funding; *Kura Oncology:* Research Funding; *Celgene:* Research Funding; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Bayer:* Consultancy; *Alexion Pharmaceuticals:* Consultancy; *Merck & Co.:* Consultancy; *Astellas:* Research Funding; *Actinium Pharmaceuticals, Inc.:* Research Funding; *Daiichi-Sankyo:* Research Funding. **Levy:** *Janssen:* Speakers Bureau; *Actinium Pharmaceuticals, Inc.:* Research Funding; *Seattle Genetics:* Research Funding; *Amgen:* Speakers Bureau; *Takeda Pharmaceuticals International Co.:* Speakers Bureau. **Park:** *Amgen:* Consultancy; *Genentech/Roche:* Research Funding; *Juno Therapeutics:* Consultancy, Research Funding. **Ravandi:** *Actinium Pharmaceuticals, Inc.:* Research Funding. **Perl:** *Actinium Pharmaceuticals, Inc.:* Research Funding; *Seattle Genetics:* Consultancy. **Smith:** *Actinium Pharmaceuticals, Inc.:* Research Funding. **Cicic:** *Actinium Pharmaceuticals, Inc.:* Employment, Equity Ownership. **Scheinberg:** *Actinium Pharmaceuticals, Inc.:* Equity Ownership, Patents & Royalties: Ac-225-Lintuzumab.

Author notes

*Asterisk with author names denotes non-ASH members.