Results of a Phase 2 Pharmacokinetic/Pharmacodynamic (PK/PD) Study of Combination Voreloxin and Cytarabine in Patients With Relapsed or Refractory Acute Myeloid Leukemia

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Background: Voreloxin, an antitumor quinolone derivative that inhibits topoisomerase II, is active in ovarian cancer and acute myeloid leukemia (AML). Nonclinical studies showed synergistic activity of voreloxin and cytarabine in vitro and in vivo (Scatena Cancer Chemother Pharmacol 2010). Methods: Phase 1b results were presented previously (Proc ASCO 2009). Phase 2 expansions studied voreloxin in combination with cytarabine in first relapsed or primary refractory AML. Dose regimens were 60 or 65 mg/m² voreloxin administered by short 15 min infusion 1–2 times per day on days 1 and 4, in combination with either 450 mg/m² ID cytarabine for 5 days or 2×10 min IV infusion 1 g/m² cytarabine (IDAC) for 5 days. Patients could complete up to 4 cycles of therapy (2 induction and 2 consolidation). Response was determined by IWG criteria. Blood, urine, and bone marrow aspirate (BMA) were collected for PK or PD analysis. Results: Safety and activity were similar for both cytarabine schedules and thus phase 2 data were pooled for 69 patients. Thirty-three patients with primary refractory AML, defined as persistent AML after induction therapy or relapsed <90 days after initial CR, and 36 patients with first relapsed AML, defined as CR > 90 days to 24 months, were studied. Most had a poor prognosis (81% primary refractoriness or first relapse with CR ≥ 12 months). The overall median age was 65 years; most patients were male, and 88% had an ECOG performance status of 0 or 1. Primary refractory patients had induction failure with a median 2 attempts (range, 1–4); first relapsed patients had a median duration of CR1 of 13.3 months. Nonhematologic grade 3 or higher adverse events ≥ 10% included upper GI mucositis (15%), febrile neutropenia (43%), sepsis, 12% pneumonia, 12%, and hypokalemia (19%). All-cause mortality was low, 2% (2 of 69) at 30 days and 9% (6 of 69) at 60 days. CR+CIPR+CIPR (OR) was 25% (20 of 69). The study population, ORR for primary refractory was 21% (7 of 33; 6 CR, 1 CRp), and for first relapse was 36% (13 of 36) (7 CR, 1 CRp, 1 CRh). For first relapse, OR was achieved in 4 patients with CR ≥ 12 months and 9 with CR ≤ 12 months (7 CR, 1 CRp, 1 CRh). Postrelease, 13 of 20 patients went to transplant and 3 received maintenance therapy with azacitidine or decitabine. One with partial remission and one with treatment failure also went to transplant; for a total of 15 of 69 patients (22%). Median survival was 216 days to 7 months (95% CI 4.8–10.1 months) and was similar for both primary refractory and first relapse; median leukemia-free survival was 329 days or 10.8 months (95% CI 7.3–7 months, not reached). Twenty of 69 patients remain in survival follow-up (range, 211–611 days), with 12 surviving ≥ 1 year or more than 1 year. PKPD, voreloxin PK was dose proportional and unaltered by cytarabine. Voreloxin elimination is nonlinear, ~ 0.5% of voreloxin total dose was in urine. DNA damage response was seen in blasts consistent with voreloxin's mechanism of action (ASH 2009). Conclusions: Activity of voreloxin in combination with cytarabine is promising in this difficult to treat patient population and was well-tolerated with a 25% ORR; median overall survival of 7.1 months, and low early mortality (5% at 30 days and 9% at 60 days). Twenty of 69 patients remain in survival follow-up, with 12 surviving ≥ 1 year or more than 1 year. The regimen allowed a bridge to bone marrow cell transplant. Safety and activity profile in this population compares favorably with recent data for other AML therapies. A multinational, randomized, double-blind, placebo-controlled, pivotal phase 3 study of voreloxin or placebo in combination with IDAC in patients with relapsed or refractory AML, after 1–2 cycles of therapy or relapsed ≥ 60 days after initial CR in 3–6 months is planned.

NON-Hematologic GRADE 3 OR HIGHER ADVERSE EVENTS ≥ 10%.

CR in patients with relapsed or refractory AML

Voreloxin can be readily combined with CIV or 2-hour IV cytarabine regimens

The combination of voreloxin and cytarabine was successfully used as a 'bridge to transplant' for relapsed/refractory patients in this study.

A multinational, randomized, double-blind, placebo-controlled, pivotal phase 3 study in relapsed or refractory AML is planned to initiate in 2H 2017


This poster and poster 8253, board #17 (single agent voreloxin in frontline, poor-risk AML) will be discussed: RM E354a 5 – 6PM.

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