

Phase I/II Trial of AEG35156 X-Linked Inhibitor of Apoptosis Protein Antisense Oligonucleotide Combined With Idarubicin and Cytarabine in Patients With Relapsed or Primary Refractory Acute Myeloid Leukemia.

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PURPOSE: X-linked inhibitor of apoptosis protein (XIAP) is an inhibitor of caspases 3 and 9 which are overexpressed in acute myeloid leukemia (AML) and may contribute to chemoresistance. We report on a phase I/II trial of the XIAP antisense oligonucleotide AEG35156 in combination with reinduction chemotherapy.

PATIENTS AND METHODS: Twenty-four patients with rapidly relapsed or refractory AML were treated with escalating doses of AEG35156 (12 to 250 mg/m²) as an intravenous solution over 2 hours and 32 patients were treated with the highest planned dose of 350 mg/m² in combination with idarubicin and high-dose cytarabine reinduction chemotherapy. Correlative studies were conducted to determine the effects of AEG35156 on levels of XIAP mRNA.

RESULTS: Knockdown of XIAP mRNA during treatment increased with the dose of the antisense. All patients who received 350 mg/m² of AEG35156 had higher than 30% target knockdown with a median maximal knockdown of 90% (range, 48% to 100%). The overall response rate was higher among the patients receiving the highest dose of AEG35156. In this group, 15 (47%) of 32 patients achieved complete response (CR)/CR with incomplete platelet count recovery (CRp) compared with only one (4%) of 24 receiving 12 to 250 mg/m² AEG35156. Among the patients receiving 350 mg/m² of AEG35156 in combination with chemotherapy, 10 (91%) of 11 who were refractory to a single induction chemotherapy regimen achieved CR/CRp after reinduction with AEG35156 and chemotherapy. AEG35156 was well tolerated save for two cases of peripheral neuropathy in patients receiving multiple doses of AEG35156.

CONCLUSION: At the highest dose tested, AEG35156 knocks down its target and appears very effective when combined with chemotherapy in patients with AML refractory to a single induction regimen.