A Phase I Study of ENMD-2076 in Patients with Relapsed or Refractory Leukemia

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BACKGROUND
ENMD-2076 is a novel, orally-active molecule that inhibits Aurora A, c-Kit, and FLT3, as well as multiple receptor tyrosine kinases that drive tumor vascularization, including VEGFR2 (KDR), PDGFR, and FGFR. A phase I study was conducted to determine the maximum tolerated dose (MTD) and toxicities of ENMD-2076 in patients with refractory hematologic malignancies.

METHODS
Patients (cohorts of 6 evaluable patients per dose level) received escalating doses of ENMD-2076 administered orally daily (225 mg (n=7), 375 mg (n=5), 525 mg (n=5), or 275 mg (n=6)). Plasma levels of ENMD-2076 were measured on Days 1, 8, & 29 of Cycle 1 and at end of study. Peripheral blood and/or bone marrow were obtained at baseline for ex vivo receptor tyrosine kinase testing and on Days 8 & 29 of Cycle 1 for pharmacodynamic (PD) monitoring to measure the effects of ENMD-2076 on cell signaling pathways. The latter flow cytometry-based assay used combined pERK, pAkt, pSTAT5, and pS6 labeling, and tested the effects of acute stimulation with SCF and FLT3 ligands in the presence or absence of pathway inhibitors, including ENMD-2076.

RESULTS
Twenty-seven patients were treated (26 AML; 1 CML-2). Median age of 69 years (range: 26-77); 14 females, 13 males; 18 patients received prior chemotherapy; 10 (37%) received 2 or more cycles of therapy. The most common non-hematological toxicities of any grade, regardless of association with drug, were fatigue, diarrhea, dysphonia, dysgeusia, hypertension, constipation, and abdominal pain. Two of 6 patients treated at the 375 mg/dose level developed dose-limiting toxicities (DLT), consisting of grade 3 fatigue. The next dose cohort was therefore decreased to 325 mg/dose; 1 patient on this dose level developed a DLT with grade 3 fatigue. However, as additional patients subsequently developed grade 2 or 3 fatigue (during cycles 1 and 2, respectively), the 325 mg/dose was not considered to be tolerable for continued administration in this patient population. The next dose cohort was therefore decreased to 275 mg/dose; 2 patients subsequently developed DLTs consistent with inhibition of the tyrosine kinases and grade 3 syncope, respectively. Overall, no patient experienced grade 4 toxicities or deaths on this treatment. Of the 20 evaluable patients, 14 patients achieved a CR (transfusion-independent with platelet counts >20,000 x 10^9/L), 2 had a CR with transfusion support, and 4 patients had an 11%, 14%, 23%, and 65% reduction in marrow blast count. Patients with untreated AML who refused induction chemotherapy or had relapsed AML after prior chemotherapy were comparable with respect to pharmacodynamic monitoring of effects of ENMD-2076.

PHARMACODYNAMIC MONITORING

Complex flow cytometry protocol developed to study multiple potential drug targets:
1) assess baseline signaling in leukemic blast cells, and
2) ex vivo drug effects on c-Kit activation, using a highly complex flow cytometry assay showing considerable inter-patient heterogeneity in baseline signaling activity, as well as the response to selective inhibitors. In a single-patient, the assay showed dose-dependent inhibition of pS6, consistent with inhibition of mutant FLT3/ITD signaling. There is also a loss of constitutive pAkt and pS6, as well as SCF-activated pERK during treatment with ENMD-2076.

CONCLUSIONS

Single agent ENMD-2076 has activity in a heavily pretreated group of AML patients that may correlate with inhibition of ERK, Akt, Stat5, and S6 activity. The recommended phase 2 dose (RPTD) in this patient population is 225 mg/dose.

BACKGROUND
ENMD-2076 is a selective inhibitor of the Aurora A kinase isoform in comparison to Aurora B (14% vs 35% SI).

METHODS
ENMD-2076 inhibits the activity of multiple kinases, including FLT3-γ, c-Kit, and CSF-1R, which are involved in hematologic malignancies.

The compound also has potent activity against receptor tyrosine kinases that are involved in angiogenesis and lymphangiogenesis, such as VEGFR2 (KDG), PDGF, and FGFR.

RESULTS

Objective response rate (ORR) was 11% (95% CI: 2-37%), of which 2 patients (8%) achieved a CRi (transfusion-independent with platelets >20,000 x 10^9/L and an MTDi of 275 mg/dose). All patients had received prior chemotherapy (median of 2; range, 1-6); 2 had received a prior autologous stem cell transplant. A total of 42 cycles were administered with a median of 1 cycle per patient (range, 0 to 8); 10 patients (37%) received 2 or more cycles of therapy. The most common non-hematological toxicities of any grade, regardless of association with drug, were fatigue, diarrhea, dysphonia, dysgeusia, hypertension, constipation, and abdominal pain. Two of 6 patients treated at the 375 mg/dose level developed dose-limiting toxicities (DLT), consisting of grade 3 fatigue. The next dose cohort was therefore decreased to 325 mg/dose; 1 patient on this dose level developed a DLT with grade 3 fatigue. However, as additional patients subsequently developed grade 2 or 3 fatigue (during cycles 1 and 2, respectively), the 325 mg/dose was not considered to be tolerable for continued administration in this patient population. The next dose cohort was therefore decreased to 275 mg/dose; 2 patients subsequently developed DLTs consistent with inhibition of the tyrosine kinases and grade 3 syncope, respectively. Overall, no patient experienced grade 4 toxicities or deaths on this treatment. Of the 20 evaluable patients, 14 patients achieved a CR (transfusion-independent with platelet counts >20,000 x 10^9/L), 2 had a CR with transfusion support, and 4 patients had an 11%, 14%, 23%, and 65% reduction in marrow blast count. Patients with untreated AML who refused induction chemotherapy or had relapsed AML after prior chemotherapy were comparable with respect to pharmacodynamic monitoring of effects of ENMD-2076.

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CONCLUSIONS

Single agent ENMD-2076 has activity in patients with relapsed or refractory hematologic malignancies.

The recommended phase 2 dose (RPTD) of ENMD-2076 in this patient population is 225 mg orally daily.

Additional flow cytometry monitoring of effects of ENMD-2076 on Aurora kinase and VEGFR2 activity is being performed (using combined staining for cyclin A2, pHistone H3 [S10], and DNA content).