The combination of GMI-1271, a potent E-selectin Antagonist in Combination with Induction Chemotherapy in Relapsed/Refractory AML: A Novel, Well-Tolerated Regimen with a High Remission Rate

Background

The treatment of patients with relapsed or refractory acute myeloid leukemia (AML) remains a significant challenge with poor outcome primarily due to low remission rates as well as short remission duration. Although allogeneic chemotherapy remains the standard approach for the treatment of patients with relapsed or refractory (R/R) AML, novel agents are urgently needed to improve clinical outcomes. The regimen consisting of mitoxantrone, etoposide, and cytarabine (MEC) is commonly used for patients with R/R AML, with remission rates of 5-30%.

E-selectin is an adhesion molecule expressed constitutively in the bone marrow endothelium which acts as a gatekeeper for cancer cells entering the bone marrow. Binding of leukemic blasts to E-selectin activates leukemic cell survival pathways, thereby contributing to chemotherapy resistance. Leukemic stem cells in the bone marrow can be resistant to cytotoxic treatment. Inhibition of E-selectin has been shown to reduce chemotherapy resistance, block cancer cells from entering the bone marrow and enhance mobilization of leukemic cells out of the bone marrow. GMI-1271 is a novel endoantibody of E-selectin, and its addition in preclinical models breaks chemotherapy resistance resulting in reduction of leukemic stem cells within the bone marrow. GMI-1271 significantly improves survival above chemotherapy alone in multiple models of AML and other hematologic malignancies.

Methods

A multi-center, open-label phase 1/2 trial enrolled adults with R/R AML receiving MEC induction chemotherapy. The primary objective was to assess the safety of escalating doses of GMI-1271 when combined with MEC: secondary objectives were to characterize pharmacokinetics (PK) and pharmacodynamics (PD), and to observe anti-leukemic activity. Eligible patients (ECOG ≥2) must have received 2 prior induction regimens, have no active CNS disease, have adequate renal and hepatic function, absolute blast count ≤100,000, and are not more than 90 days post-HCT. Adjunctive treatment with GMI-1271 at increasing doses was administered concomitant with chemotherapy (24 hours prior, throughout, and 48 hours post MEC). MEC consisted of mitoxantrone 10 mg/m², etoposide 150 mg/m², and cytarabine 1000 mg/m² IV for 5 days, supportive care was given as per institutional guidelines. Dose limiting toxicity (DLT) was assessed at count recovery or Day 44 whichever came first. DLT was defined as either persistent neutropenia and/or thrombocytopenia beyond day 44 in the absence of disease; OR any grade 3 non-hematologic toxicity that did not resolve to Grade 2 by day 44. End of Treatment (Day 44 or count recovery if earlier), bone marrow was assessed for remission of leukemia. No formal hypothesis testing was done compared to historical control overall remission rate of 25% was done using one-sided exact binominal analysis and the Clopper and Pearson method to 90% CI.

Results

Pharmacodynamics

Plasma levels of GMI-1271 following a single dose were analyzed over the treatment period in all dose groups. This response is seen both in mean area-under-the-curve (AUC). A dose-related difference was not seen, suggesting all dose levels may be above the plateau for an anti-leukemic effect.

Pharmacokinetics

Peripheral CD34+ cells, including both hematopoietic stem cells and leukemic blasts, were not observed to increase in the 24 hours after treatment with a steady dose of GMI-1271. Total peripheral CD34+ counts varied widely and were noted to be higher in subjects with high blast and absolute blast count, but did not change after GMI-1271 administration.

Pharmacokinetic profile and dose-proportionality were consistent with previous healthy volunteer studies, with the exception that clearance was 28% lower in patients with AML in this study. Clearance of GMI-1271 in a typical 50-kg-old subject was 1.28 L/h. In patients >60 years, GMI-1271 decreased in peak level by 27% compared to ≤12 months. GMI-1271 remained above therapeutic levels for a year or more, as a function of changes in creatinine clearance. Cmax and daily Area-Under-Curve (AUC) at steady state are shown as a function of age and dose.

Current Study Status

We report the Phase I clinical assessment of novel E-selectin antagonist GMI-1271, in combination with one cycle of induction chemotherapy (MEC), in heavily pretreated, high-risk patients with relapsed/refractory AML.

Safety

The combination of GMI-1271 with MEC chemotherapy is well tolerated.

Conclusions

No Dose Limiting Toxicities (DLTs) have been observed in all 3 cohorts evaluated: (n=5) peripheral counts, including neutrophils and platelets, recovered by Day 44 in patients achieving remission.

PRRD

• Reduction in all-e-selectin plasma levels confirmed on-target activity for all dose levels

GMI-1271 plasma levels were above levels associated with anti-leukemic activity in animals model of AML.

Clinical Outcomes

• AML overall survival rate (CR) at 47% was observed; Complete Remission Rate was 42%.

This is higher than expected given the high-risk cytogenetic and disease features in this group.

Remission duration was sufficient to allow patients to proceed to salvage stem cell transplant (N=6).

References