Abstract 3286

ADMINISTRATION OF THE DUAL E-SELECTIN/CXCR4 ANTAGONIST, GMI-1359, RESULTS IN A UNIQUE PROFILE OF TUMOR MOBILIZATION FROM THE BONE MARROW AND FACILITATION OF CHEMOTHERAPY IN A MURINE MODEL OF FLT3 ITD AML

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Background

A drawback of the current standard of care with chemotherapeutic agents is that these drugs tend to be ineffective at accessing and killing cancerous cells in the bone marrow, thereby reducing the treatment’s overall potency. Recently, E-selectin and the CXCR4 ligand, CXCL12 have been shown to be constitutively expressed in vascular niches in the bone marrow where they co-localize and bind with leukemic cells thereby protecting these cells from the effects of chemotherapy drugs. With the limited penetration of bone marrow where they co-localize and bind with leukemic cells thereby protecting these cells from the effects of chemotherapy drugs. With the limited penetration of bone marrow where they co-localize and bind with leukemic cells thereby protecting these cells from the effects of chemotherapy drugs.

Introduction

GMI-1359 is a rationally-designed parenteral small molecule glycomimetic (MW = 1115) with dual antagonistic activity to ligands for E-selectin (CXCL4) and CXCR4. We recently reported that targeting CXCR4-selective E-selectin with GMI-1359 showed efficient mobilization of AML blasts in to the circulation, and significant prolonged survival of mice in a KIT-ITD mutant mouse xenograft 1.

Results

GMI-1359 was assessed for inhibition of cell cell binding to immobilized E-selectin and CXCR4 antibodies binding to subject cells. E-selectin binding was quantified.

Table 1. Competitive Binding Activity (IC50) of GMI-1359 Against E-selectin and CXCR4

<table>
<thead>
<tr>
<th>Compound</th>
<th>E-selectin</th>
<th>CXCR4</th>
</tr>
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<tbody>
<tr>
<td>GMI-1359</td>
<td>1.05</td>
<td>&lt;1.0</td>
</tr>
</tbody>
</table>

Summary

- The small molecule glycomimetic, GMI-1359, inhibits ligand binding to both E-selectin and CXCR4 with approximately equipotent potencies.

Table 2. Comparative activity of Glycomimetic and AMD-3100 in the Cerebromatch® SafetyScreen® assay

![Table 2](null)

The inhibitory/antagonistic activity of 10 µM GMI-1359 and 10 µM AMD-3100 was evaluated in enzyme and radioligand binding assays. Significant responses were defined by >50% inhibition/inhibition.

Conclusion

- The profile of GMI-1359 induced tumor cell mobilization is distinct from both plerixafor (rapid mobilization of short duration) and E-selectin antagonist (gradual mobilization of long duration).
- As E-selectin but not CXCR4 has been reported to be critical for tumor cell entry into the BM, the sustained presence of tumor cells in circulation after GMI-1359 treatment could be the result of blocking not only CXCR4 but also E-selectin, thereby inhibiting their re-entry into the BM.
- This novel kinetic signature of mobilization by dual inhibition of two important adhesion molecules and accompanying improvement in survival over standard chemotherapy support the potential for combination with current treatments to improve outcomes for patients with marrow involved disease.
- In human trials have been initiated.

References


Figure 1A. Efficacy of GMI-1359 in Combination with AraC/DNR in MV4-11 Tumor Bearing NRC Mice – Dose Response

Female NCr mice (4-7 wks of age) were injected i.p. with MV4-11 (1x10^6 cells/mouse), and beginning 7 days post injection, treated t.i.d. for 5 days with saline (0 mg/kg), dexamethasone (5 mg/kg, i.p.); or a combination of GMI-1359 (80, 40 and 20 mg/kg, i.p.) and DNR/DAUNO (Figure 1A). Mice reacted similarly between saline and dexamethasone groups with limited survival improvements. Nonetheless, mice survived more than 70 days after treatment with GMI-1359 administered at 80 mg/kg (n=4). Survival response was monitored in some patients with hematological malignancy. Disruption of malignant cellular interactions with either E-selectin or CXCR4 would ablate bone marrow sequestration and re-homing, and mobilize cancer cells out of the bone marrow into the blood stream, making them more susceptible to cytotoxic chemotherapy.

Figure 2. Mobilization Profile of MV4-11 AML Cells from the Bone Marrow Following a Single IP Administration of GMI-1359, E-selectin antagonist or AMD-3100

A comparison of tumor mobilization by GMI-1359 to E-selectin or CXCR4 antagonists was determined in NCR mice with established Bile infiltrative MV4-11 ITD human AML tumor (modeling in vivo leukemic burden). Since E-selectin binds (LeX) to GMI-1359 (94 mg/kg), and CXCR4 binds (RANTES) to GMI-1359 (44 mg/kg), a potent E-selectin antagonist (44 mg/kg), or placebo (0 mg/kg) and blood samples were harvested for flow cytometry of multiple targets for AML cells, i.e. CD11b and MHC (mouse CD24).

Figure 3. Efficacy of GMI-1359 in Combination with AraC/DNR in MV4-11 Tumor Bearing NRC Mice – Impact of Interval Dosing

Time post injection (hrs) | Percent survival
---|---
0 | 100
30 | 80
60 | 50
90 | 20
120 | 0

Table 3. Toxicokinetic Parameters of the NOAEL in Rat and Monkey after a 1 hour IV Infusion

<table>
<thead>
<tr>
<th>Species</th>
<th>NOAEL (mg/kg)</th>
<th>Tmax (h)</th>
<th>Area under the curve (mg*h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>30</td>
<td>1.5</td>
<td>3000</td>
</tr>
<tr>
<td>Monkey</td>
<td>80</td>
<td>1.5</td>
<td>3000</td>
</tr>
</tbody>
</table>

Summary

- This NOAEL in monkey was 40 mg/kg due to transient clinical observations with no significant pathological findings at doses up to 80 mg/kg.
- The NOAEL in rat was 10 mg/kg for males and 40 mg/kg for females due to histologic findings in the kidney of male rats and clinical observations in female rats.
- Clinical observations in rat and monkey were similar and comprised hyperactivity, tremors, partial closure of the eyes and dilated pupils.
- Toxicokinetics evaluation in rat and monkey showed that the compound increased in exposure, no apparent difference between sexes, and no accumulation 28 days of daily administration.
- GMI-1359 was tested for off-target interactions, mutagenicity, and clastogenicity with no significant findings observed.
- DMMA studies indicated a low likelihood of significant liver metabolisms, no interactions with P-gp as substrate or inhibitor, moderate binding to plasma proteins and good plasma stability.
- Taken together the non-clinical toxicology and DMMA profile of GMI-1359 support entry into human clinical studies.

Figure 2A and 2B shows the effect of GMI-1359 alone or in combination with AraC/DNR on mobilization of leukemic cells in circulation. The pharmacodynamics of GMI-1359 was evaluated in female CD-1 mice. Dosing was performed in triplicate for each time point. Each mouse received a single bolus dose into the peritoneal cavity at time zero on the day of dosing. Blood samples were collected up to 24 h post treatment. The pharmacokinetics of GMI-1359 was evaluated in fasted male CD-1 mice. Dosing was performed daily administration via one hour IV infusions for 28 days followed by a 14 day recovery period.

Figure 3A and 3B show the effect of GMI-1359 alone or in combination with AraC/DNR on mobilization of leukemic cells in circulation. The pharmacodynamics of GMI-1359 was evaluated in female CD-1 mice. Dosing was performed in triplicate for each time point. Each mouse received a single bolus dose into the peritoneal cavity at time zero on the day of dosing. Blood samples were collected up to 24 h post treatment.

References