Comparison of the PI3K- Inhibitors TGR-1202 and GS-1101 in Inducing Cytotoxicity and Inhibiting Phosphorylation of Akt in CLL Cells in vitro

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Abstract

It is commonly complicated by cytopenias and infections.

The PI3K/Akt pathway is known to be a central mechanism by which CLL lymphocytes survive and evade apoptosis. It is known that constitutive activation of Akt promotes CLL lymphocyte survival, while inhibition of the Akt pathway induces CLL lymphocyte death.

There are four isoforms of PI3K, and expression of the δ isoform of PI3K is largely restricted to lymphocytes. Clinical evaluation of PI3K-δ inhibitors, such as GS-1101, has been promising, with responses seen in relapsed and/or refractory CLL patients.

TGR-1202 is a novel PI3K-δ specific inhibitor previously demonstrated to inhibit Akt phosphorylation and induce apoptosis in B-cell lymphoma cell lines.

METHODS

1. Chronic lymphocytic leukemia (CLL) is classically defined as an indolent B-cell malignancy. However, patients may require repeated therapies for progressive disease.
2. Despite numerous available therapies, clinical responses may be incomplete and/or of relatively short duration. Therapy is commonly complicated by cytopenias and infections.

RESULTS

Table 1: Patient Sample Characteristics and Prognostic Markers

<table>
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<tr>
<th>Patient</th>
<th>%IgM</th>
<th>IgG</th>
<th>IgD</th>
<th>ZAP70</th>
<th>CD38</th>
<th>FISH</th>
<th>DBl Time (days)</th>
<th>IGHV Status</th>
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<td>76</td>
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<td>pos</td>
<td>neg</td>
<td>neg</td>
<td>13q</td>
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<td>12q</td>
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</table>

Figure 1: Induction of cytotoxicity in primary CLL cells after 3 days of incubation with TGR-1202 is dose-dependent and is equivalent to GS-1101.

Figure 2: Induction of apoptosis in primary CLL cells after 2 days of incubation with TGR-1202 is dose-dependent and is equivalent to GS-1101.

Figure 3: Akt is phosphorylated after cross-linking of the B-cell receptor by anti-immunoglobulin (‘Ig Stim.’). The addition of TGR-1202 or GS-1101 returns Akt phosphorylation to baseline (‘Control’) at concentrations between 0.1 to 1.6 μM.

CONCLUSIONS

1. TGR-1202 is a PI3K-δ inhibitor that suppresses Akt phosphorylation and induces apoptosis-dependent cytotoxicity in primary CLL cells.
2. The total number of individual patients who provided primary cells is relatively small, yet significant alterations in Akt phosphorylation, apoptosis induction, and cytotoxicity were seen after incubation with TGR-1202.
3. Preliminary, we observed equal in vitro efficacy of TGR-1202 in CLL lymphocytes with high versus low risk prognostic markers.
4. TGR-1202 is equally efficacious to GS-1101 with regards to in vitro induction of apoptosis and toxicity, and in suppressing Akt phosphorylation.
5. Our results suggest that TGR-1202 is an effective PI3K-δ inhibitor in CLL in vitro, and thus may have benefit as a potential therapy for treating CLL patients.

REFERENCES