Myelosuppression in Patients Treated With the Telomerase Inhibitor Imetelstat Is Not Mediated Through Activation of Toll-Like Receptors

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INTRODUCTION

The human telomerase enzyme (TE) plays a critical role in maintaining cell immortalization and is implicated in the expansion of tumor cells. Telomerase inhibitors such as imetelstat are under clinical evaluation as potential therapeutic agents for patients with myeloproliferative neoplasms (MPN) who have excessive platelet production. Imetelstat inhibits cellular telomerase activity in vitro, but it has not been characterized whether it also reduces telomerase activity in megakaryocyte (MK) precursors in vivo. We have previously shown that imetelstat has limited effects on non-malignant MK precursors, and we hypothesized that imetelstat’s effects on MPN MK precursors may be mediated through Toll-like receptors (TLRs) and P2Y12.

OBJECTIVE

To investigate whether imetelstat inhibits MKs and reduces thrombocytopenia in murine models and clinical samples.

RESULTS

TLR Activity

TLR activity was measured in murine bone marrow and human MK precursors and was found to be unaffected by imetelstat. Interestingly, we observed that the concentration of imetelstat required to inhibit telomerase activity in human MK precursors was similar to the concentration required to inhibit telomerase activity in MPN MK precursors (Table 1).

RESULTS

Table 1. TLR activity and spliceosome subunit expression in murine MK precursors treated with imetelstat.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>TLR activity</th>
<th>Spliceosome subunit expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Imetelstat 7.5 µM</td>
<td>75</td>
<td>80</td>
</tr>
<tr>
<td>Imetelstat 15 µM</td>
<td>50</td>
<td>60</td>
</tr>
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</table>

CONCLUSIONS

Imetelstat does not inhibit MKs and therefore does not impair MK maturation. However, imetelstat reduces MK production in patients with MPN, suggesting a potential role for imetelstat in the management of thrombocytosis. These findings provide important insights into the mechanisms underlying the drug’s inhibitory effects on platelet production.

ACKNOWLEDGMENTS

This work was supported by Janssen Research & Development, LLC. The authors are grateful to the patients who participated in this study and to the members of the Janssen Research & Development, LLC, Clinical Development Organization for their support.

REFERENCES


Table 1. Imetelstat inhibits cellular telomerase in patients with ET treated with imetelstat (15 µg/kg - 7.5 µg/kg) in a phase 2 study of 240 patients.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Cellular telomerase inhibition</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>100</td>
</tr>
<tr>
<td>Imetelstat 7.5 µg/kg</td>
<td>75</td>
</tr>
<tr>
<td>Imetelstat 15 µg/kg</td>
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ACKNOWLEDGMENTS

Sponsored by Janssen Global Services, LLC.