Dose individualization of indisulam to reduce the risk of severe myelosuppression

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Introduction

Indisulam:
• An investigational anticancer drug.
• Currently in phase II clinical development.
• Myelosuppression is dose-limiting.
• Treatment with indisulam is complicated by wide interpatient variability regarding drug exposure and severity of myelosuppression.

Aim:
• To investigate the impact of patient-related covariates on PK-PD parameters related to indisulam-induced hematological toxicity.
• To identify patients at risk of developing severe myelosuppression.
• To develop an algorithm for dose individualization of indisulam.

Methods

Data:
• 7 phase I studies and 6 phase II studies.
• 412 patients.

PK-PD model:
• Previously developed structural model (Fig1).
• Indisulam concentrations, neutrophil and thrombocyte counts simultaneously analyzed.

Covariate analysis:
• Covariate analysis according to a pre-specified plan: only plausible relationships were evaluated.
• Demographics, physical condition, prior treatment, concomitant medication, CYP2C genotype and biochemistry.

Evaluation of clinical relevance:
• Simulation study to determine the relative risk of dose limiting myelosuppression for the 2.5 and 97.5 percentiles of each patient characteristic versus the median.
• A relative risk of less than 0.9 or more than 1.1 was considered clinically relevant.

Development of a dosing algorithm:
• The correlation between patient characteristics and the risk of severe neutropenia was minimized.

Results

Table 1: Statistically significant covariate relationships and their clinical relevance.

<table>
<thead>
<tr>
<th>Pharmacokinetetic covariates</th>
<th>Related parameter</th>
<th>Covariate effect</th>
<th>Relative risk (RR) of dose limiting haematological toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>body surface area (m²) and WT (kg)</td>
<td>( V_{max} )</td>
<td>( (\text{BSA}^2 + \text{WT})^{1/2} )</td>
<td>Japanese: RR= 1.19, heterozygous: RR= 1.15, homozygous: RR= 1.38</td>
</tr>
</tbody>
</table>

Table 2: Algorithm for dose individualization.

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Score 1</th>
<th>Score 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: Female</td>
<td>-3</td>
<td>3</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CYP2C genotype: wildtype</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>heterozygous CYP2C*3</td>
<td>-2</td>
<td>-2</td>
</tr>
<tr>
<td>homozygous CYP2C*3</td>
<td>-4</td>
<td>-4</td>
</tr>
<tr>
<td>CYP2C19*2 or *3</td>
<td>-6</td>
<td>-6</td>
</tr>
<tr>
<td>CYP2C19 wildtype</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Japanese</td>
<td>-1</td>
<td>1</td>
</tr>
<tr>
<td>Baseline neutrophil count: (&lt;4.10^9/L)</td>
<td>-5</td>
<td>-5</td>
</tr>
<tr>
<td>(&gt;4.10^9/L)</td>
<td>-5</td>
<td>-5</td>
</tr>
<tr>
<td>Total score</td>
<td>total score 25</td>
<td>total score 25</td>
</tr>
<tr>
<td>Individual dose (mg/m²)</td>
<td>775 + 500</td>
<td>375</td>
</tr>
</tbody>
</table>

Example 1: application of the dosing algorithm for a Caucasian male patient with a wildtype genotype and a high baseline neutrophil count of 9⋅10⁹/L → 900 mg/m².

Example 2: application of the dosing algorithm for a Japanese female patient with a CYP2C19*2 or *3 genotype and a normal baseline neutrophil count → 375 mg/m².

Conclusion

• This study has identified patient characteristics related to an increased risk of severe myelosuppression after therapy with indisulam.
• Dose individualization based on these patient characteristics may contribute to treatment optimization.

References

[1] Zandvliet et al. JPP 2006