An Extended Semi-Physiological Myelosuppression Model following Docetaxel administration with Improved Simulation Properties

BACKGROUND

- The semi-mechanistic myelosuppression model by Friberg et al. has successfully described the time-course of both leukocytes and neutrophils following several different anti-cancer drugs.
- Nonetheless, the model has difficulties in capturing the rapid drop in neutrophil counts following Docetaxel treatment as depicted by VPC (Fig 1b).
- More information of the haematological system may be gained by a simultaneous analysis of leukocytes (WBC) and neutrophils (NEU) since leukocytes consist mainly of neutrophils (60-70%).

OBJECTIVES

To improve the predictive capacity of the semi-mechanistic myelosuppression model for neutrophil counts following docetaxel treatment, by refining the model structure and incorporate more knowledge of the haematological system.

METHODS

Patients
- 601 cancer patients
- Diagnosis: carcinoma, melanoma and sarcoma
- Single course of docetaxel in monotherapy (no G-CSF)
- Dose: 75 or 100 mg/m², 1 hour infusion
- 3549 pairwise observations of WBC and NEU
- Individual PK-profiles were generated using a population PK-model

Population PK-PD modeling
- Data analysis: NONMEM Vi with FOCE INTER
- Data was Box-Cox transformed with a factor of 0.2

Model development
1. A BASIC model describing NEU and WBC simultaneously using a published semi-mechanistic myelosuppression model have been developed
2. An EXTENDED model where each structural component of the BASIC model was optimized to improve the description of the neutrophil time-course.

RESULTS

Basic Model
- Two myelosuppression-models: one for NEU and one for non-NEU
- Allowing different parameter values for NEU and non-NEU
- WBC was modeled as: CircWBC = CircNEU + Circnon-NEU
- A linear drug model: Edrug = Slope * CDrug
- The half-life in blood was fixed to the literature value of NEU (7 h)
- Residual error: additive on a Box-Cox scale with ETA on EPS

Extended Model
- The significant (p<0.001) improvements of the model structure:
  - A sigmoidal Emax model for the drug effect was significant for both NEU and non-NEU
  - A feedback function mimicking the reduction in maturation time in transition compartments, and a blood circulation compartment. The cells are eliminated from the blood pool by random movement of cells into the tissue (kcirc).
- These modifications greatly improved the model’s capability to capture the nadir value as determined by a visual predictive check (Fig 1) and resulted in a total drop in OPV by 88%

CONCLUSION

- A simultaneous analysis of the time-course of neutrophils and leukocytes was successfully performed.
- The docetaxel data supported a more complex model for the neutrophils which yielded more precise predictions of the time-course of the neutrophil counts.
- The model can be useful in illustrating the differences between the cell types and allow prediction of neutrophils from leucocyte measurements.

Table 1. Final parameter estimates from the BASIC and EXTENDED model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BASIC model</th>
<th>EXTENDED model</th>
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<tbody>
<tr>
<td>Non-Neutrophils</td>
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<td>non-NEU0</td>
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<td>MMT</td>
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<td>T1/2blood</td>
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<td>Residual error</td>
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<td>0.49</td>
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<tr>
<td>RSE%</td>
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<td>11</td>
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</tbody>
</table>

IIV, interindividual variability expressed in CV
RSE%, relative standard error obtained by bootstrap (80 samples)