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Phase I study design of indisulam: evaluation and optimization

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Introduction

Phase I program indisulam:

- Indisulam: anticancer drug with dose-limiting neutropenia.
- Phase I dose escalation studies have been performed to define a safe dose.
- 4 administration schedules have been evaluated in 4 parallel studies.

Hypothesis:

- A two-stage model-based clinical trial design may optimize the efficiency of phase I clinical development of novel anticancer agents.
- PK-PD modeling of one initial phase I study (stage 1) may be used for selection of an optimal starting dose for subsequent studies (stage 2).

Aim:

- To evaluate, retrospectively, if a two-stage model-based design would have been safe and efficient for the phase I clinical development of indisulam.

Methods

Data:

4 phase I studies:

1. Dx1: single 1-hour infusion, 3-weekly
2. Dx5: 1-hour infusion days 1-5, 3-weekly
3. Wx4: 1-hour inf. days 1,18,15,22, 6-weekly
4. 120H: 120-hour infusion, 3-weekly

Analysis plan:

1. Development of 4 **PK-PD models** using data from each phase I study
2. Prediction of **optimal starting dose** for other phase I studies based on PK-PD models from step 1
3. Evaluation of starting doses regarding:
   1. **safety**: are all starting doses below the highest administered dose?
   2. **efficiency**: reduction of the number of patients treated at a dose level below the recommended dose?

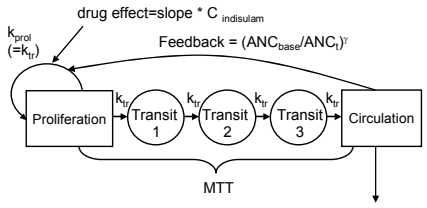


Figure 1: Structural model of indisulam-induced neutropenia.[1-3]

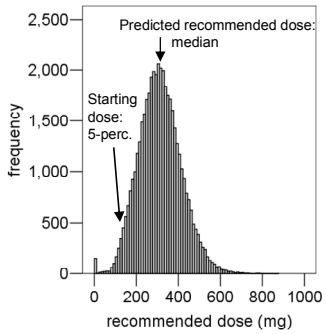
PK-PD model development:

- PK model: evaluation of 1-,2-,3-cmt models distribution and elimination: linear/saturable
- PD model: semi-physiological model of neutropenia (Fig.1) with Bayesian priors (MTT=116h ± geometric CV 18%, γ=0.167 ± 20%, IIV MTT=22.4% ± 59%)

Selection of starting dose for future studies:

- dose escalation studies were simulated:
  - modified Fibonacci-like dose escalation
  - 3- and 6-patient cohorts
  - DLT: grade 4 neutropenia during >7 days
- 200 x 200 simulations for each scenario:
  - to account for parameter uncertainty: 200 PK-PD parameter sets selected from PK-PD parameter estimates + covariance
  - to account for variability between patients: 200 replicate simulations for each PK-PD parameter set and different seed
- starting dose for future study: 5-percentile of simulated recommended doses

Results



Highest dose level with <2 out of 6 patients developing dose-limiting neutropenia

Figure 2: Distribution of 40,000 recommended doses and determination of the proposed starting dose (5-percentile). The variability comprised variability between patients and uncertainty of PK-PD parameter estimates.

PK-PD model:

- PK model: 3-cmt models
  distribution: linear + saturable
  elimination: linear for Dx1 and linear + saturable for Dx5, Wx4, 120H
- PD model: Bayesian priors improved the stability of the PD model, especially for weekly dosing.

Evaluation of starting doses:

- All model-based starting doses were below the highest administered dose and were higher than the conventional starting doses.
- Out of 65 patients treated at dose levels below the recommended dose, 14 (120H), 22 (Dx5), 28 (Wx4) or 33 (Dx1) patients were redundant using the two-stage model-based design (Figure 3).

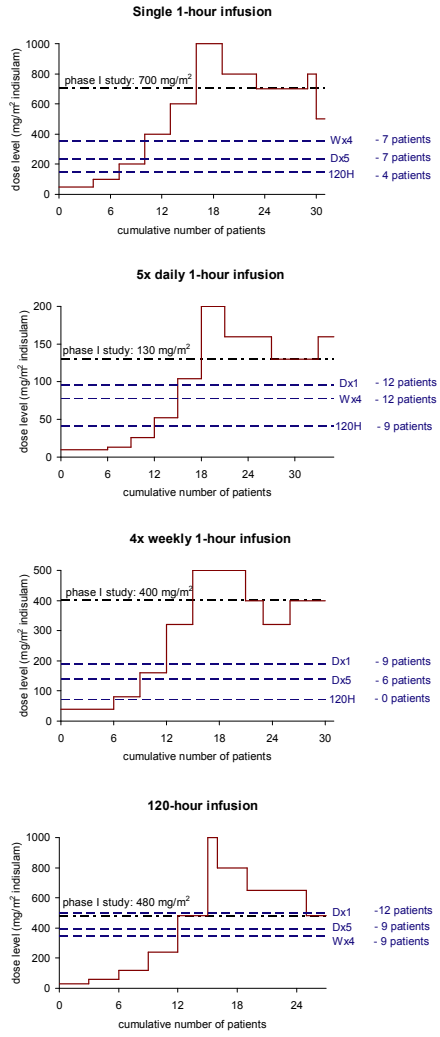


Figure 3: Phase I studies of indisulam: course of dose escalation and proposed starting doses based on data from each of the other 3 regimens.

Conclusion

- A two-stage model-based clinical trial design could have reduced the number of patients treated with indisulam at dose levels below the recommended dose by 14 to 33 patients = 22% to 51%.
- The design may improve study efficiency, seems safe and does not interfere in the conduct of trials.
- The two-stage model-based design is currently being evaluated in extensive simulation studies.

References

[1] Van Kesteren et al. JCO 2002
[2] Friberg et al. JCO 2002
[3] Van Kesteren et al. Invest New Drugs 2005