Influence analysis explores heterogeneity in database before data processing by a parametric population method

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Presentation

Retrospective analysis of data from clinical studies in metastatic breast cancer

Dependent variable: sum of the longest diameter of metastatic sites measured

No pharmacokinetics (only administration protocols)

Data available [1, 2, 3]:

Phase II: Capecitabine C (n=168)

Phase III: Doxtaxel D (n=223) vs. D+C (n=222)

Already treated [4, 5, 6]

Objectives

Control homogeneity in PK-PD population data by using influence analysis (leave-one-out procedure)

Assess interaction for drugs used in combination

Tools

NONMEM V.6, Matlab

THE DATA

C Single agent

Phase II

n=168

D Single agent

Phase III

n=223

C+D Combination

Phase III

n=222

MODELING

Global modeling

\[
\frac{d(\text{KL})}{dt} = -KPC \cdot \gamma(t) \cdot \omega(t)
\]

\[
\frac{d(\text{KL})}{dt} = -KPD \cdot \omega(t)
\]

\[
\frac{d(y_1(t))}{dt} = KL \cdot \omega(t) \cdot \left( \text{KDC} \cdot \exp(-\text{DMC} \cdot t) \right) + \text{KDD} \cdot \exp(-\text{DMD} \cdot t) \cdot \gamma(t) \cdot \omega(t)
\]

Model explanations:

- \( \gamma(t) \) (t): “Effective dose” for C and D respectively
- \( \omega(t) \): Administration protocols for C and D respectively
- \( K_{PC} \): Fixed biopharmaceutical constants
- \( n_0 \): Tumor size

- Estimated parameters:
  - \( KL \]): Proliferation parameter (max tumor size : \( n \) [mm], fixed)
  - \( DM \) : Resistance parameter distinct for each drug
  - \( KD \): Constant cell kill rate distinct for each drug
  - \( n_0 \): Initial tumor size

Combination: the model

Families of models tested for combination

- F1: all parameters (fixed parameters and random effects)
- F2: without random effect on KLD
- F3: KLD and/or DMD
- F4: KKD and/or DMD
- F5: DMD removed
- F6: DMD removed and without random effect on DMD
- F7: DMD removed
- F8: DMD and DMD removed

Best models in F5, F6

Retained model in F6

\[ F_6 \]

\[ F_5 \]

\[ F_7 \]

\[ F_8 \]

Combination: influence analysis and mixture model

Leave-one-out

DMD and KDC scatter plots reveal two subpopulations (fig7).

Mixture

Best mixture models when subpopulations are defined with KL and DMD : \( x_1 = 0 \) and \( x_2 = 1 \) are verified [7].

Significant decrease in OFV as compared to the model without mixture (confirmed by AIC).

Individual OFV are obtained (KL, KDC, KDD, DMD, \( n_0 \)).

Leave-one-out vs. Mixture

Mixture partition the population in different sets than leave-one-out do.

In both cases, DMD parameter is different in the two subpopulations.

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CONCLUSION

1. In a previous work [6], the resistance was reported to the proliferation term. Presently, resistance is reported to the cell kill term and models fit better to data.

2. Combination and single-agent models involve different mechanisms. In the combination model:
   - no resistance for C,
   - no random effect for D.

3. Leave-one-out reveals two subpopulations. This heterogeneity was confirmed with the mixture model.

4. D resistance is the parameter responsible of the obtained partitions.

5. Partitions of individuals by the two methods are different and more investigations are in process.

6. Experimental protocols don’t influence the partitions obtained.

7. As compared to single agents, combination reveals enhanced efficacy for D (interaction not characterized at the moment).