Therapeutic Drug Monitoring for Tyrosine Kinase Inhibitors. Possibilities, difficulties, and challenges

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PURPOSE

Therapeutic drug monitoring and dose individualization can contribute to increased benefits for patients by augmenting the efficacy and/or decreasing the risk of toxicity. Therapeutic drug monitoring is especially interesting for drugs exhibiting a highly variable exposure between patients and a small therapeutic window.
For numerous drugs, such as Kinase Inhibitors or Animoglycosides, clear relationships between exposure and treatment outcome have been established, thus allowing for the definition of target exposure values. scale in hospital care.

OBJECTIVE

Dose individualization has been more and more advocated over the years, the lack of dedicated, user-friendly and reliable decision-support software hampers its use on a large scale in hospital care. We present dose-recommendation tools for two TKIs (sunitinib and imatinib) and the results of their retrospective application on therapeutic drug monitoring hospital data.
The application permits to:
- Take all available information in a rigorous mathematical framework into account.
- Remove logistic constrains: the drug measurement does not need to be at steady-state, nor just before the next dose

TWO-STEP METHOD FOR DOSE ADAPTATION

Step 1: Determine pharmacokinetic parameters of the patient and calculate actual PK profile

The goal of this step is to find the individual pharmacokinetic parameters representing the patient. Each PK parameter is represented by a distribution, that describes not only the most likely value, but also the associated uncertainty.
To this end, we integrate the information from a population PK model (usually a model from the literature, recalibrated on internal data), patient covariates if relevant (age, sex, weight, …), and individual drug measurements.
Based on this information, we compute the conditional distributions of the PK parameters of the patients. These distributions then permit to predict the actual PK profile of the patient along with its uncertainty.

Step 2: Use these parameters to perform simulations of alternative doses

Simulations of new doses taking into account operational constraints (such as available tablet doses) are performed using the estimated individual parameters.
The purpose is not to find the best one, but to simulate many possible ones and represent the associated uncertainty .

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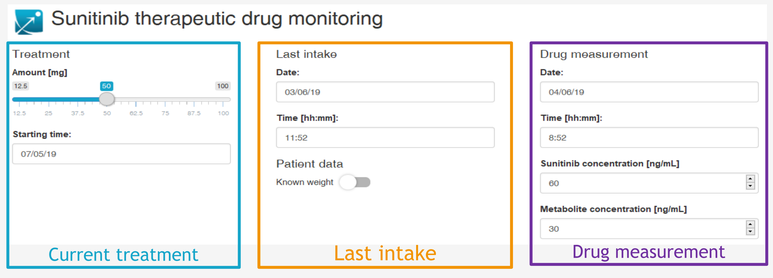

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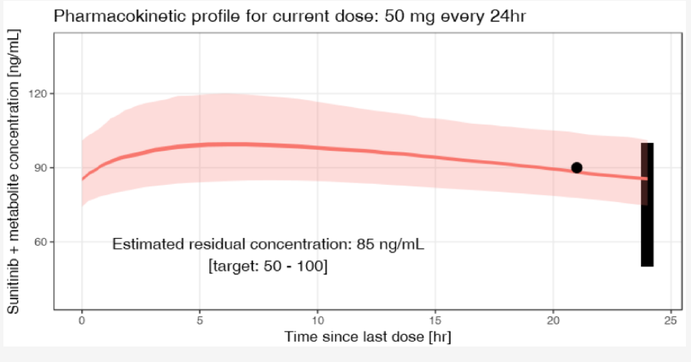

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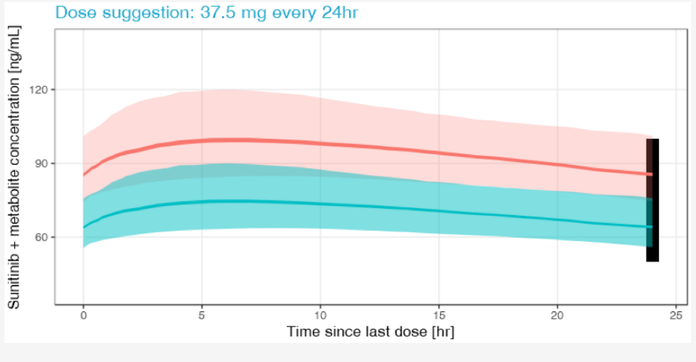

CONCLUSION

We have applied our dose-recommendation application to the therapeutic drug monitoring (without adaptation) data base of the Cochin Hospital (Paris, France). The data base records around 900 sparse PK measures for 233 cancer patients followed during several weeks.

The application recommended to maintain the standard dose for only 16% of the patients, while the recommended dose was below the standard for 67% and above the standard for the remaining 17%.

Drug amount (mg)	Percentage (%)
12.5	3
25	29
37.5	35
50	16
62.5	10
>75	7

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