Dose individualization potential for oral targeted oncolytics

dr. Neeltje Steeghs
Therapeutic drug monitoring

TDM has shown its benefits in many drug classes (e.g. anticonvulsants, antibacterials, antipsychotics, antidepressives, immunosuppressants and antiretrovirals). However, in cancer treatment, TDM is still limitedly applied

WE HAVE TO CHANGE THIS!
Disclosures

• Medical Oncologist and Clinical Pharmacologist at Netherlands Cancer Institute

• I am involved in studies and research projects funded by pharmaceutical companies

• Part of this work is supported by unrestricted grants of Novartis, Roche and Pfizer
There is new ammunition in the war against cancer. These are the bullets.

Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we’ve been waiting for?
THERAPEUTIC DRUG MONITORING

What is it?

drug selection

fixed dose

one-size-fits-all approach

THERAPEUTIC DRUG MONITORING
What is it?

Strong rationale....

✓ Small therapeutic window
✓ Strong PK/PD relationship
✓ High interindividual variability (and low intraindividual variability??)
✓ No relevant easily measurable biomarker
✓ Bioanalytical assay available

→ The case for many oral targeted anticancer drugs
PROBLEMS WITH THE CURRENTLY USED FIXED DOSES

30% of patients are underdosed

15% of patients are overdosed

Development of TDM infrastructure in NKI 2010-2019

1. Definition of PK targets
2. Development of feasible dosing strategies
3. Development and validation of bioanalytical assays
4. Training of clinical pharmacologists to support TDM program
5. Initiation of national implementation study
Example: pazopanib PK-PD

\[ C_{\text{min}} \geq 20.5 \text{ mg/L} \rightarrow \uparrow \text{PFS} \]

52.0 vs. 19.6 weeks \((p=0.0038)\)
Practical Guidelines for Therapeutic Drug Monitoring of Anticancer Tyrosine Kinase Inhibitors (TKIs) on the Pharmacological Level: An Update

Huixin Yu · Neeltje Steeghs · Jan H. M. Schellens · Jos H. Alwin D. R. Huitema

Therapeutic Drug Monitoring of Oral Anti-Hormonal Drugs in Oncology

Stefanie L. Groenland · Merel van Nuland · Remy B. Verheijen · Jan H. M. Schellens · Jos H. Beijnen · Alwin D. R. Huitema · Neeltje Steeghs

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Abstract Oral anti-hormonal drugs are essential in the treatment of breast and prostate cancer. It is well known that the inter- and intrasubject variability in pharmacokinetics of these drugs is substantial. Pharmacokinetic exposure could be targeted (exemestane: minimum plasma concentration \( C_{\text{min}} \) \( 4.1 \) ng/mL and anastrozole: \( C_{\text{min}} \) \( 0.1 \) ng/mL). However, for most drugs, no validated guidelines exist for therapeutic drug monitoring (TDM) in oncology. This review aims to provide insights into the TDM of oral anti-hormonal drugs in order to optimize treatment and patient outcomes.

Despite the fact that pharmacokinetic-pharmacodynamic data can contribute to individualized therapy, therapeutic drug monitoring (TDM) has not been widely adapted in oncology. This review aims to provide insights into the TDM of selected oral anti-hormonal drugs in order to optimize treatment and patient outcomes.
Dosing strategy: pazopanib

- Complex pharmacokinetic profile
- Insoluble at pH > 4
- Two phases of absorption?
  1. Rapid absorption at beginning of intestine
  2. Slow absorption

Yu et al (Clin Pharmacokin, 2016)
Simulations based on population pharmacokinetic model

Splitting intake moments:
- 75% increase in $C_{\text{min}}$
- 59% increase in $\text{AUC}_{0-24h}$

Yu et al (Clin Pharmacokin, 2016)
Results clinical trial

Groenland et al. ASCO 2019
TDM strategy

1. Check compliance
2. Check drug-drug interactions
3. Consider cost-neutral options:
   - Splitting intake moments
   - Co-administration with food (abiraterone)
   - Co-administration of boosters (not yet implemented)
4. Increase dose
PROSPECTIVE STUDY

Therapeutic drug monitoring of oral anticancer drugs

Primary outcome

- To halve the proportion of patients with a low pharmacokinetic exposure after 12 weeks (compared to historical data)

Secondary outcomes

- Feasibility and tolerability of TDM
- Efficacy (compared to historical data): PFS, ORR
- Physician adherence > 90%

Groenland et al. ESMO 2019
### LIST OF STUDY DRUGS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Corresponding Drug</th>
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<tr>
<td>Abiraterone</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Alectinib</td>
<td>Nilotinib</td>
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<td>Vemurafenib/cobimetinib</td>
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<tr>
<td>Gefitinib</td>
<td>Vismodegib</td>
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</table>

* dose recommendations only for trametinib
HOW TDM TARGETS WERE DEFINED

Preferably based on **exposure-response analyses**

If not available yet:

- **mean/median exposure**

*PK-targets generally 82% of average population concentration*

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METHODS: STUDY DESIGN

In case of low exposure and acceptable tolerability a PK-guided intervention is recommended.

PK-guided interventions could include:
- emphasizing compliance
- adjusting concomitant medication due to drug-drug interactions
- concomitant intake with food (abiraterone, pazopanib)
- splitting intake moments (pazopanib)
- conventional dose increments

Inclusion:
- W4 W5-6
- W8 W9-10
- W12 W13-14
- W24 W25-26

Groenland et al (Ther Drug Monit, 2019)
PATIENT INCLUSION

Open for inclusion: June 1st 2017 – present
Data cut-off: August 1st 2019

369 patients included

350 patients with PK data available

246 patients evaluable for primary endpoint

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients</th>
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<tbody>
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<td>Imatinib</td>
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</table>
RESULTS: OVERVIEW

153 of 350 patients ≥ 1 low PK

83 of 153 patients PK-guided intervention

67 of 83 patients successful

67% toxicity n = 47

13% discontinuation n = 9

11% physician adherence n = 8

9% logistics n = 6
RESULTS: IMATINIB (GIST)

- **Evaluation**: Imatinib patients (n=54)
- Adequate PK: C_min ≥ 1100 ng/mL (n=17)
- No toxicity: 400 mg QD (n=13)
- Toxicity: dose reduction (n=4)
- PK-guided intervention: (n=28)
- No PK-guided intervention: (n=9)
- Not feasible due to toxicity: (n=6)
- Physician adherence: (n=3)
- Compliance emphasized
- Dose increased to 600 mg QD (n=20)
- Dose increased to 400 mg BID (n=7)
- Not feasible due to toxicity (n=6)
- Physician adherence (n=3)
CONCLUSIONS

• 44% of patients is underdosed at a certain time point during treatment;

• PK-guided dose optimization is feasible in clinical practice;

• In the majority of patients, PK-guided interventions resulted in target attainment without additional toxicities;

• The effect of TDM on treatment efficacy still needs to be evaluated;

• Efforts should be made to implement TDM of oral anticancer drugs in routine care → real life data of these patients should be collected
Future plans

- Keep TDM protocol up-to-date
- Include more patients
- Add more hospitals
- Implementation in standard of care

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44% of patients is underdosed

**can**

WE HAVE TO CHANGE THIS!
DPOG (www.dpog.nl)

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