Pharmacokinetics, pharmacodynamics and pharmacogenetics of metronomic chemotherapy

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“Indeed, metronomic chemotherapy may be better defined as a frequent, regular administration of drug doses designed to maintain low, but active, range of concentrations of chemotherapeutic drugs during prolonged periods of time \textit{without inducing excessive toxicities}.”

Bocci & Kerbel. \textit{Nat Rev Clin Oncol} 2016 \textit{in press}
Pharmacokinetics of metronomic chemotherapy: the neglected part of the story

Despite more than 10 years of clinical studies on metronomic chemotherapy, very few clinical pharmacokinetic data are currently available

**WHY?**

**Methodological issues** such as long-term sampling, availability of proper detecting methods (e.g. 4-OH-CTX), combinations of drugs

The **underestimation** of the importance of the relationship between plasma/tumor concentrations of metronomic drugs (and their active metabolites) and clinical activity
Pharmacokinetics: a key aspect for the development of metronomic concept

The **pharmacokinetic knowledge** about metronomic chemotherapy regimens is **essential** to determine:

1. a dose schedule that reaches an **active** concentration of drug

2. the main mechanisms of action involved in the success of metronomic chemotherapy at a **specific range of drug concentrations** in plasma

3. **pharmacodynamic markers** in oncology patients for such drug concentrations

4. any possible **pharmacokinetic interactions (positive or negative)** with other drugs, such as tyrosine kinase inhibitors or therapeutic antibodies
Metronomic cyclophosphamide PK /PD

**Metronomic daily oral dose: 20 mg/kg**

- Antiangiogenic activity
  - ↓ number of vessels in matrigel plug
  - ↓ number of viable CEP

**Intermittent metronomic schedule: 140 mg/kg every 6 days**

- Activation of antitumor innate immunity
  - ↑ number of macrophages, dendritic cells and NK cells

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Chen CS et al. Neoplasia 2014;16: 84

Emmenegger et al. Mol Cancer Ther 2007;6:2280
No available data about the active metabolites of cyclophosphamide (e.g. 4-OH-CTX) and description of PK only after a single dose.
Metronomic cyclophosphamide PK/PD - III

Daily oral dose CTX 50 mg

Antiangiogenic activity

Patients with lower VEGF levels after 2 mo of treatment had higher PFS

Prostate cancer

Breast cancer

Responder patients had lower VE-cadherin expression


Intermittent metronomic schedule
Cyclophosphamide 100 mg/day, 1 week on and 1 week off

CTX and 4-OH-CTX concentrations

Metronomic cyclophosphamide regimen selectively depletes CD4^+CD25^+ regulatory T cells and restores T and NK effector functions in end stage cancer patients

Pharmacokinetics of metronomic oral vinorelbine

**Standard dose** 30 mg/m² i.v. $\rightarrow C_{\text{max}}$ 1130±636 ng/ml


**A**

vinorelbine displayed linear pharmacokinetics


the blood $C_{55}$ for vinorelbine was attained after 14 days of treatment, and this compound did not show any evidence of accumulation during months of successive treatment
Metronomic oral vinorelbine PK/PD - I

Antiangiogenic activity
↓ plasma VEGF
↑ plasma TSP-1

Day 28

Vinorelbine 30 mg p.o. three times a week in prostate cancer patients

Bocci et al. 2016 unpublished data
Metronomic oral vinorelbine PK/PD - II

Vinorelbine 30 mg p.o. three times a week in prostate cancer patients

Immunological-mediated mechanism?

After 4 weeks of treatment, non responder patients showed increased plasma concentrations of the soluble form of B7-H3, an inhibitor of prostate cancer immunity

Metronomic UFT PK/PD

5-FU 370 mg/m² i.v. → C$_{\text{max}}$ 48.41±7.69 µg/ml


Allegrini, Di Desidero et al. Angiogenesis 2012, 15: 275

daily dose of 100 mg UFT p.o in combination with CTX 50 mg

< plasma VE-cadherin in SD
> plasma TSP-1 in SD

Antiangiogenic activity

VE-cadherin
Pharmacokinetic parameters could be predictive of metronomic chemotherapy success?

**Cut-off = 0.501 µg/ml**

*Sensitivity = 81.82%*

*Specificity = 76.92%*

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**PFS according to 5-FU Cmax at day 1**

- Cmax 5-FU > 0.501*
  - Median PFS: 4.5 ms (95%C.I. 1.5-7.5)
- Cmax 5-FU < 0.501*
  - Median PFS: 2 ms (95%C.I. 0.1-3.9)

*R: ROC curve

Log-rank P=0.0222

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**OS according to 5-FU Cmax at day 1**

- Cmax 5-FU > 0.501*
  - Median OS: 9.5 ms (95%C.I. 5-14)
- Cmax 5-FU < 0.501*
  - Median OS: 5.65 ms (95%C.I. 3-8.3)

*R: ROC curve

Log-rank P=0.0172

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Allegrini, Di Desidero et al. Angiogenesis 2012,15:275
Despite the limitation of this analysis due to the small number of patients, these results identified a **pharmacokinetic cut-off value** in a clinically relevant population.

UFT pharmacokinetic parameters may be used from the **very first administration** of the drug to predict the efficacy and the survival of colorectal patients undertaking the metronomic schedule.

...and capecitabine?
Metronomic capecitabine

**Capecitabine** 1250 mg/m² p.o. → $C_{\text{max}}$ 10.74±6.77 µg/ml

Bocci et al. unpublished data

**Which is the prevalent mechanism of action for these drug concentrations?**

- Direct cytotoxic activity on tumor cells
- Antiangiogenic activity
- Activation of antitumor innate immunity

PK of 1 patient

dose of 800 mg capecitabine p.o

Bocci et al. 2016 unpublished data

Farkouh et al. Anticancer Res. 2014;34:3669

Pharmacokinetic interactions between topotecan and pazopanib in patients

Turner et al. Anticancer Res 2013, 33:3823

Kerklaan et al. Br J Cancer 2015, 113:706

Significant differences of topotecan PK at standard doses

NO significant differences of topotecan PK at metronomic doses

Turner et al. Anticancer Res 2013, 33:3823
Pharmacokinetic interactions between metronomic topotecan and pazopanib in preclinical studies

Kumar et al. Clin Cancer Res 2011, 17:5656

Jedeszko et al. Sci Transl Med 2015, 282ra50

NO significant differences of topotecan PK at metronomic doses

but...

Increased intracellular accumulation of topotecan in cancer and endothelial cells
Is the *genetic background* involved in the efficacy or resistance to metronomic therapies?

Gene *polymorphisms* as possible predictive biomarkers for metronomic chemotherapy

Are *somatic mutations* of tumors involved in the efficacy or resistance to metronomic therapies?

?
Prostate cancer patients harbouring the germline **VEGF -634CC** genotype were not responsive to metronomic cyclophosphamide

Clinical response: decrease of PSA≥50%

<table>
<thead>
<tr>
<th>genotype</th>
<th>% of survival</th>
<th>Progression-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CC</strong></td>
<td>48.84%</td>
<td>VEGF -634 CC: median PFS 2.2 ms (C.I. 95% 0.45-3.95)</td>
</tr>
<tr>
<td><strong>CG/GG</strong></td>
<td>39.53%</td>
<td>VEGF -634 CG/GG: median PFS 6.25 ms (C.I. 95% 3.28-8.62)</td>
</tr>
</tbody>
</table>

**Median PFS 2.2 vs. 6.3 months**

A possible hypothesis from this pilot study....

Hypothesis

Could be the beginning for a personalized metronomic chemotherapy?

Urgent need for a prospective validation trial...
but metronomic chemotherapy is given in combination with an antiangiogenic drug and after MTD chemotherapy...

It will be the same?
Conclusions

1) Different metronomic drug concentrations - and schedules - may determine different prevalent mechanisms of action (selection of therapy and patient based on the prevalent effect?)

2) Pharmacokinetic parameters should be extensively investigated in relation to pharmacodynamics (PK/PD approach)

3) Therapeutic drug monitoring (TDM) of metronomic chemotherapy to maintain drug concentrations in the “activity range”

4) Randomized, prospective, pharmacogenomic/pharmacogenetic clinical studies should be performed to achieve a personalized metronomic chemotherapy
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