Individual prediction-based dose adaptation of capecitabine: 

*in silico* comparison with the standard method, impact on limiting toxicity and on antitumour efficacy

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EMR 3738 “TherapeutiC Targeting in Oncology”
Faculty of Medecine Lyon Sud, France

20th PAGE meeting, Athens, 9 June 2011
Introduction

- 5-FU:
  - inhibitor of cell cycle
  - one of the most used anticancer drugs for the treatment of solid tumors (colorectal, breast) (since 1957)

- Capecitabine (Xeloda®, Roche):
  - prodrug of 5-FU taken orally (a blockbuster since 2002)
  - main toxicity: **hand-and-foot syndrome** (54% patients)
    (redness, peeling, numbness, pain of the skin of palms and soles)

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>None</td>
<td>Tingling or burning</td>
<td>Pain</td>
<td>Severe pain</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Skin damage</td>
<td>None</td>
<td>Mild redness, swelling; skin intact</td>
<td>Redness, swelling; skin intact</td>
</tr>
</tbody>
</table>
Evolution of the Hand-and-foot syndrome

600 patients, 2500 mg/m²/day, 1 year

Probability

P (Grade 3)
P (Grade 2)
P (Grade 1)
P (Grade 0)

Dose adaptation strategies

**Standard:**
If grade $\geq 2$, treatment stopped until HFS returns to grade $\leq 1$. Subsequent doses are changed according to the table:

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<td></td>
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</tr>
<tr>
<td>2</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>75%</td>
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Dose adaptation strategies

**Standard:**
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<td>100% 75% 50% 0</td>
</tr>
<tr>
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<td>100% 75% 50% 0</td>
</tr>
<tr>
<td>3</td>
<td>75% 50% 0 0</td>
</tr>
</tbody>
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**Alternative:**
individualized adaptation according to model-based prediction of patient-specific toxicity risk
Objectives of this work

**Develop** an individual prediction-based dose adaptation method using a model for *ordinal* observations that results in **less toxicity** without reducing **efficacy** as compared to the standard dose reductions.

**Compare** its performance to that of the standard practice:

- impact on HFS toxicity
- impact on antitumour efficacy

➔ by randomized *in silico* clinical trials
Individual prediction-based dose adaptation

Population
HFS model
Individual prediction-based dose adaptation

Indiv. observations
(doses, grades, covar.)

Population
HFS model

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Individual prediction-based dose adaptation

Indiv. observations (doses, grades, covar.)

Population HFS model

Individual HFS model
Individual prediction-based dose adaptation

Indiv. observations (doses, grades, covar.)

Indiv. HFS model

Population HFS model

Prediction of severe toxicity risk over next 3 weeks
Individual prediction-based dose adaptation

Indiv. observations (doses, grades, covar.)

Individual HFS model

Prediction of severe toxicity risk over next 3 weeks

Individualized dose for the next cycle

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Individual prediction-based dose adaptation

Indiv. observations (doses, grades, covar.)

Population HFS model

Individual HFS model

Prediction of severe toxicity risk over next 3 weeks

Individualized dose for the next cycle

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Dose-toxicity model: the principle

Individual prediction-based dose adaptation

- **Indiv. observations** (doses, grades, covar.)
- **Population HFS model**

**Individual HFS model**

**Prediction of severe toxicity risk** over next 3 weeks

**Individualized dose** for the next cycle
Dose determination rules

**Target:**
Average predicted probability of HFS grade ≥2 over next cycle (3 weeks) ≤ **Target Risk**

**“Individualized” dose:**
Daily dose closest to this target,

constrained to be at least 50%
and at most 100% or 150% of the nominal dose
(depending on the protocol and HFS history)
Reducing the severity and frequency of adverse effects is desirable, but what if the anticancer effect is reduced as well?

→ Need to incorporate a model of effect on tumours
Colorectal tumour inhibition model

Tumour(s) measure: sum of largest tumour diameters (mm)

In silico clinical trial

3 parallel arms according to dose adaptation method:
- Standard
- Basic individual risk prediction-based
- Advanced individual risk prediction-based

Common features for all arms:
- **50,000** virtual patients per arm.
- **Dosing regimen:** 2500 mg/m²/day for 2 weeks, 1 week rest.
- **Max 30 weeks** (10 cycles of 3 weeks).
- **Interruption** of treatment in case of grade ≥2 HFS, until recovery to grade ≤1.
- Next doses are reduced according to the corresponding protocol.
- **Definitive end of treatment:**
  - if HFS grade ≥2 lasts for more than 6 consecutive weeks,
  - if HFS grade ≥2 appears for the 4th time,
  - if disease progression is observed,
  - if complete response is observed and the patient has received 6 treatment cycles.
- HFS is monitored for 4 weeks after the treatment is ended.
In silico clinical trial: simulation of tumour and HFS observations

- Covariate values were simulated from distribution estimated from clinical trial data used to build the corresponding models.

- HFS grade observations were obtained for each week by random sampling according to grade probabilities defined by the model.

- Tumour observations were obtained every 6 weeks.

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*RECIST: Response Evaluation Criteria In Solid Tumours
# Dose adaptation protocols

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<th>Protocols</th>
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<td>-</td>
<td>-25% after 2\textsuperscript{nd} occurrence of G\geq2</td>
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<td></td>
<td>-50% after the 3\textsuperscript{rd} occurrence of G≥2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0% after the 4\textsuperscript{th} occurrence of G≥2</td>
<td></td>
</tr>
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<td><strong>Basic</strong></td>
<td>After the 1\textsuperscript{st} occurrence of at least G1, if the risk of G≥2 exceeds the TR</td>
<td></td>
<td>Corresponding to predicted average risk of G≥2 over next 3 weeks ≤ 6%</td>
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<td>prediction-based</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Advanced</strong></td>
<td>After the 1\textsuperscript{st} occurrence of at least G1, if the risk of G≥2 exceeds the TR</td>
<td></td>
<td>Corresponding to predicted average risk of G≥2 over next 3 weeks ≤ 4%</td>
<td>Before G≥2: [50%, 150%]</td>
</tr>
<tr>
<td>prediction-based</td>
<td></td>
<td></td>
<td></td>
<td>After G≥2: [50%, 100%]</td>
</tr>
<tr>
<td></td>
<td>If stable disease &amp; no HFS (start after 4 cycles) or if ≥6 weeks in G1 and no G≥2</td>
<td></td>
<td></td>
<td></td>
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*20\textsuperscript{th} PAGE meeting, Athens, 9 June 2011*
RESULTS:
Performance of adaptation protocols
Results: impact on *toxicity*

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of weeks with G≥2 (all patients / only those having G≥2)</th>
<th>% of patients having G≥2</th>
<th>% of patients having reoccurring events with G≥2</th>
<th>Duration of reoccurring events with G≥2 (weeks)</th>
<th>% of patients who dropout due to HFS</th>
</tr>
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<tbody>
<tr>
<td><strong>Standard</strong></td>
<td>5.2 / 8.1</td>
<td>55.5%</td>
<td>13.6%</td>
<td>5.7</td>
<td>23.2%</td>
</tr>
<tr>
<td><strong>Basic</strong></td>
<td>3.9 / 6.9</td>
<td>55.6%</td>
<td>13.1%</td>
<td>5.4</td>
<td>22.4%</td>
</tr>
<tr>
<td><strong>Advanced</strong></td>
<td>3.8 / 6.8</td>
<td>55.2%</td>
<td>12.6%</td>
<td>5.0</td>
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## Results: impact on efficacy

<table>
<thead>
<tr>
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<th>% of responders</th>
<th>Relative change from baseline (median)</th>
<th>% of patients who have disease progression</th>
</tr>
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<tbody>
<tr>
<td>Standard</td>
<td>49.2%</td>
<td>-23.3%</td>
<td>31.7%</td>
</tr>
<tr>
<td>Basic</td>
<td>49.4%</td>
<td>-23.3%</td>
<td>31.7%</td>
</tr>
<tr>
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Dynamics of the distributions of the HFS grades
Examples of "Advanced" method

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Tested variations of prediction-based dose adaptations

- Target risks: 4%, 5%, 6%
- Allowing dose reductions down to 25% of nominal dose
- Allowing dose increases up to 125% of nominal dose
- Time of starting dose increases: after 2 cycles
- Allowing dose increases only if no HFS was observed
- Lower target risk for increases than for reductions
- Lower target risk for reductions if patient has tumour response (only if 95th percentile of predicted tumour size at the next scan does not correspond to disease progression)
CONCLUSIONS about capecitabine dose adaptation results

Individual prediction-based dose adaptation on the basis of HFS grade observations was developed and showed to be:
- slightly superior in terms of HFS toxicity and
- equivalent in terms of efficacy

The benefits on average could be:
- **10 days** for duration (by reducing the frequency and length of reoccurring events with G≥2)
- **7%** for dropouts due to HFS
Obstacles & perspectives for dose adaptation based on **ordinal** variable

**Estimates** of individual random effects (EBEs) are **poor** due to:

- categorical data being poor in information,
- low identifiability of the dose-toxicity grade relationship (observed values of response-driving variable are too small to identify the toxic effect function well),
- uneven distribution of grades within-subject.

[Paule et al. Empirical Bayes estimation of random effects of a mixed-effects proportional odds Markov model for ordinal data. Computer Methods and Programs in Biomedicine (in press)]

However, for this model, poor EBEs did not have a significant impact on the results because the **probabilities** of HFS grades are highly **insensitive to dose changes**

Higher impact of prediction-based dose adaptation based on ordinal variable is expected for **reversible** toxicities with **faster dynamics** (e.g. gastrointestinal)
Acknowledgements

The colleagues from EMR3738 Therapeutic Targeting in Oncology:
Michel Tod, Emilie Hénin, Benoit You, Gilles Freyer, Pascal Girard

for funding my PhD studies

for providing the capecitabine toxicity data of two Phase III trials
Thank you!
Backups
Criteria for comparison of dose adaptation strategies

Concerning **HFS toxicity:**
- Number of weeks with HFS grade ≥2
- % of patients having reoccurring events with G≥2
- Duration of reoccurring events with G≥2
- % of patients who drop out due to HFS

Concerning **anticancer effect:**
- % of patient having tumour response
- % of patients who have progression of disease (→dropout due to lack of efficacy)
- Relative change from baseline of tumour sizes
Statistical power analysis

100 replications of trials with
- 300 patients per arm
- 350 patients per arm
- 600 patients per arm

Wilcoxon rank sum test used to test the difference in severe toxicity duration

CONCLUSION:
350 patients per arm would be needed for a clinical trial to achieve at least 90% statistical power to demonstrate a difference in severe HFS duration at \( \alpha = 0.05 \).
Population dose-toxicity model
mixed-effects transitional proportional odds model for ordinal data

\[
\frac{dQ}{dt} = Dose - K_i \cdot Q, \quad K_i = K \cdot e^{\eta_i}
\]

\[
\text{logit}[P(Y_{it} \leq 0 \mid Y_{i(t-1)} = G^*)] = B_0^* - \frac{E_{\text{MAX}}^* \cdot (Q_{it} \cdot K_i)}{ED_{50} + (Q_{it} \cdot K_i)} + (CLcr_i - 75.5) \cdot \theta_{CLcr} + \eta_{2i}
\]

\[
\text{logit}[P(Y_{it} \leq 1 \mid Y_{i(t-1)} = G^*)] = B_0^* + B_1^* - \frac{E_{\text{MAX}}^* \cdot (Q_{it} \cdot K_i)}{ED_{50} + (Q_{it} \cdot K_i)} + (CLcr_i - 75.5) \cdot \theta_{CLcr} + \eta_{2i}
\]

\[
P(Y_{it} \leq C \mid Y_{i(t-1)} = C^*) = \frac{\exp(\text{logit})}{1 + \exp(\text{logit})}
\]

\[
p_{i0} = P(Y_{it} = 0) = P(Y_{it} \leq 0)
\]

\[
p_{i1} = P(Y_{it} = 1) = P(Y_{it} \leq 1) - P(Y_{it} \leq 0)
\]

\[
p_{i1} = P(Y_{it} = 2) = P(Y_{it} \leq 2) - P(Y_{it} \leq 1) = 1 - P(Y_{it} \leq 1)
\]

\textbf{a priori information:} \quad \Theta = (B_0^0, B_1^0, B_0^1, B_1^1, B_0^2, B_1^2, E_{\text{MAX}}^0, E_{\text{MAX}}^1, E_{\text{MAX}}^2, ED_{50}, K, \theta_{CLcr})

\[
\begin{pmatrix}
\eta_1 \\
\eta_2
\end{pmatrix} \sim N(0, \Omega), \quad \Omega = \\
\begin{bmatrix}
\omega_{11} & \omega_{12} \\
\omega_{12} & \omega_2
\end{bmatrix}
\]

**In silico clinical trial: doses**

- Capecitabine is available in tablets of **150 mg** and **500 mg**

- Daily doses are **rounded** to values recommended in prescription guidelines (so that even amounts can be taken in the morning and in the evening):
  - 3000, 3300, 3600, 4000, ... , 5600 mg
  (+ reduced doses: 1000, 1300, ...)

- Both models assume that dosing is **2500mg/BSA once a day**
  (the real dosing is 1250mg/BSA twice a day)
In silico clinical trial: simulation of Hand-and-foot syndrome

- **Basal creatinine clearance** simulated from a lognormal distribution, restricted to be in [27, 219]
  \[
  \text{logCLcr} \sim \text{N}(\text{mean} = 4.34, \text{SD} = 0.349), \text{CLcr} = \exp(\text{logCLcr})
  \]

- **BSA** simulated from a normal distribution, restricted to be in [1.19, 2.5]
  \[
  \text{mean} = 1.82, \text{SD} = 0.227
  \]

- **Individual ETA** values are simulated from a bivariate normal distribution as reported for the HFS model

- **HFS grade observations** are obtained for **each week** by random sampling according to grade probabilities defined by the model

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**In silico** clinical trial: simulation of tumour size and disease status

- **Baselines** simulated from a lognormal distribution, restr. to min 10 mm
  \[ \text{logbase} \sim N(\text{mean}=4.25, \text{SD}=0.5), \text{baseline} = \exp(\text{logbase}) \]

- **Observations every 6 weeks**, with an assumed proportional measurement error:
  \[ \text{observation} = \text{true value} \times \exp(\text{error}), \text{error} \sim N(\text{mean}=0, \text{SD}=0.025) \]

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*RECIST: Response Evaluation Criteria In Solid Tumours*
Transitions between grades (once a week)
(600 patients)
Grade probabilities

P(G≥2)  P(G=1)  P(G=0)
Estimation of individual random parameters

Bayesian estimation approach *Maximum A Posteriori* (MAP) is used for estimation of individual parameters on the basis of individual’s observed data and population model.

**Ind. observ.** (grades, doses, CLcr)

**Population** model and parameters

Maximization of MAP function

**Estimates** of individual parameters
Estimation of individual random parameters

Implementation of the \textbf{MAP method}:

\[
\hat{\eta}_{i\text{MAP}}(H_{it}) = \text{Arg} \left[ \max_{\eta_i} \frac{p(\eta_i) \cdot p(H_{it} | D_{it}, H_{it-1}, CLcr_i, \Theta, \eta_i)}{p(H_{it})} \right]
\]

\textbf{Likelihood (of ordinal observations)}:

\[
p(H_{it} | D_{it}, H_{it-1}, CLcr_i, \Theta, \eta_i) = \prod_{j=1}^{t} \prod_{g=0}^{2} p_{ijg}^{y_{itg}}
\]

\[
y_{itg} = \begin{cases} 
1, & \text{if } Y_{it} = G, \\
0, & \text{otherwise}; 
\end{cases} \quad \text{where } G = \{0, 1, \geq 2\}
\]

\textbf{Maximization by Simplex}
Simulation of the trial

- Simulated individual parameters
  - Dose
  - Preceding grade
  - Creatinine clearance
  - Toxicity grade

MODEL-based adaptation
- Estimation of individual parameters
- Calculation of the dose for the next cycle

STANDARD adaptation
- Occurrence of severe toxicity
- Fraction of the nominal dose

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<thead>
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<th>Occurrence of severe toxicity</th>
<th>Fraction of the nominal dose</th>
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<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>100%</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>75%</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>50%</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt;</td>
<td>0</td>
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Colorectal tumour inhibition model

\[
\frac{dy(t)}{dt} = k_{\text{growth}} \cdot e^{n_1} \cdot y(t) - \text{dose}(t) \cdot k_{\text{drugkill}} \cdot e^{n_2} \cdot e^{-\lambda \cdot t} \cdot y(t)
\]

\(y(t)\) – sum of largest tumour diameters (mm), time is weeks

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<tr>
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<th>CV</th>
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<tr>
<td>(k_{\text{growth}})</td>
<td>0.021</td>
<td>80%</td>
</tr>
<tr>
<td>(k_{\text{drugkill}})</td>
<td>0.025</td>
<td>69%</td>
</tr>
<tr>
<td>(\lambda)</td>
<td>0.053</td>
<td>159%</td>
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\[\sqrt{\sigma} = 11.83 \text{ (mm)}\]

Simulated tumour dynamics
Results of “Advanced” method if true ETAs or population values were used

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<td>5.0</td>
<td>21.6%</td>
<td>49.4%</td>
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</tr>
<tr>
<td>Advanced True ETAs</td>
<td>3.7 / 6.6</td>
<td>55.0%</td>
<td>12.5%</td>
<td>4.8</td>
<td>20.5%</td>
<td>49.1%</td>
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<td>33.0%</td>
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<tr>
<td>Advanced No ETAs</td>
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<td>12.4%</td>
<td>5.2</td>
<td>22.0%</td>
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PPC for transitions