The time course of tumour size changes with gemcitabine

What can we learn about pharmacology?

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Outline

• What does Pharmacology mean?
• The War on Cancer
• Tumor response Study
  – A pharmacodynamic model for the time course of tumor shrinkage in patients with ‘big cell’ lung cancer
• Tumour size and Survival
• Drug Development Strategy
PK = Pharmacokinetics: What the body does to the drug
PD=Pharmacodynamics: What the drug does to the body
Rx=Treatment: What the prescribed and patient need to know.

The ‘new’ War on Cancer

Kennedy, Hutchison call for new war on cancer

Calling for a renewed war on cancer, Senators Edward M. Kennedy of Massachusetts and Kay Bailey Hutchison of Texas introduced legislation today designed to improve research and treatment.

In a joint article, the two senators point out that since the United States declared the original war on cancer in 1971, the mortality rate has decreased by only 4 percent, far less than for heart disease and stroke.

"Why We’re Losing the War on Cancer”

Accelerating Anticancer Agent Development and Validation Workshop June 20-22, 2007

Keynote Address: “Learning Too Little, Too Late: Why We Need a New Paradigm for the Cancer Clinical Trial”

Clifton Leaf
Former Executive Editor
Fortune

We do clinical trials to LEARN—as quickly as possible—which treatments have the best shot of working.
Resisting RECIST

Appendix V. Table 3. Definition of best response according to WHO or RECIST criteria

<table>
<thead>
<tr>
<th>WHO</th>
<th>RECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance, confirmed at 4 weeks*</td>
</tr>
<tr>
<td>PR</td>
<td>30% decrease, confirmed at 1 month*</td>
</tr>
<tr>
<td>SD</td>
<td>Neither PR nor PD criteria met</td>
</tr>
<tr>
<td>PD</td>
<td>25% increase, or PR, or SD documented before increased disease</td>
</tr>
</tbody>
</table>

*WHO = World Health Organization; RECIST = Response Evaluation Criteria in Solid Tumors; CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease.

Throwing away data?

Singapore Infusion Rate Study
‘Big Cell’ Lung Cancer

- Open Label, Randomized, phase II trial
- Gemcitabine (28 patients in each arm):
  - days 1 and 8 every 3 weeks x 6 cycles
  - Arm A: 750 mg/m² over 75 minutes
  - Arm B: 1000 mg/m² over 30 minutes
- Carboplatin:
  - Target AUC of 5 mg/mL/min
  - given on day 1 of each cycle prior to the gemcitabine infusion
- No differences in:
  - response rate (primary endpoint)
  - survival (secondary – not powered)


Hypothesis is that formation of CTP is saturable and thus high infusion rates may be less effective because of saturation of formation of active substance. This then leads to the objective of this study to test the hypothesis. However, note that this design confounds dose and duration of infusion.

Tumour Size Measurements

- 261 measurements of tumour size
  - Largest dimension of the primary tumour measured from CT images using electronic calipers
  - Used only for RECIST category in primary publication
  - ‘Discovered’ during gemcitabine PK analysis
- Measurements at protocol baseline, cycles 2, 4 and 6, and bimonthly
  - Actual mean follow up 3.5 months
Gemcitabine Pharmacology

- Gemcitabine (dFdC)
  - Inactive pro-drug
- dFdCTP (gemcitabine triphosphate)
  - Intracellular, active, tri-phosphate metabolite
- dFdU
  - Major extracellular, inactive metabolite

Exposure Response

- Which Exposure Measure?
  - Dose
    - Cannot distinguish PK from PD causes of variation
  - AUC
    - Can be used to identify causes of PK variability through model linking Dose to AUC
    - Discards information about time course of concentration
  - C(t)
    - Can distinguish PK from PD variability
    - Can be used to describe and predict schedule dependence

Why Dose by Dose Concentration Time Course, C(t), Won’t Work

- Concentration Spikes With Each Cycle
- Slow Tumour Response
How to Describe Drug and Tumour Time Course?

- What Determines the Wash Out of Drug Effect?
  - “KPD” model for pharmacokinetics without concentration
  - What “apparent half-life” of drug would explain the effect time course?
  - Can be based on Dose or AUC
  - C(t) not required

- Why is Tumour Response to Drug Delayed?
  - Time course of tumour response takes weeks
  - Time course of drug concentration is complete within a few hours
  - Binding of drug to DNA probably rapid
  - Effect of DNA damage on cell proliferation probably slow
  - Takes time for damaged/dead cells to be removed

Since a delay exists between tumor response and drug administration, the time course of exposure to drug at the tumor effect site was described by an apparent half-life using a “KPD” model. The KPD model assumes drug is administered as a bolus amount (the dose) which is eliminated with an apparent half-life ($T_{1/2,\text{effect}}$) that explains the time course of effect.

Tumour Size Model

Tumour Growth Rate

\[
\frac{d\text{Size}}{dt} = (\text{Rate In} \times \text{Size}) - \frac{1}{T_{\text{turnover}}} \times \text{Size}^2
\]

Tumour Turnover Kinetics

Simple Feedback

Semi-mechanistic

Natural history of tumour growth has rapid growth with asymptote

Feedback inhibits growth

KPD Drug Effect and Tumour Turnover

- Effect assumed to slow rate of proliferation of new tumour cells

Dose

\[
\text{Effect}(t) = 1 - \frac{\text{max}}{T_{\text{turnover}}} \times \text{Size}^2
\]

Drug Effect Model

KPD Model

\[
\frac{d\text{Size}}{dt} = \text{Growth} \times \text{Effect}(t) - k_1 \times \text{Size}^3
\]

Tumour Size Model

\[
T_{\text{1/2,\text{effect}}} \text{ describes delay in drug effect}
\]

\[
T_{\text{turnover}} \text{ describes delay in tumour response}
\]
**Slide 16**

KPD plus Turnover

![Graph showing Tumour Size and Effective Amount of Drug (Ae) over time.]

**Slide 17**

Variability in Gemcitabine Dose-Response

![Graph showing variability in gemcitabine dose-response with different colors representing observed and predicted values.]

**Slide 18**

Tumour Size Turnover and Pharmacodynamics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Final Estimate</th>
<th>BSV %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size&lt;sub&gt;b&lt;/sub&gt;, tumour size at baseline (cm)</td>
<td>6.7</td>
<td>54.6</td>
<td>(5.7, 7.8)</td>
</tr>
<tr>
<td>T&lt;sub&gt;turnover&lt;/sub&gt;, Tumour turnover* (week)</td>
<td>1.6</td>
<td>24.7</td>
<td>(0.3, 2.64)</td>
</tr>
<tr>
<td>Dose&lt;sub&gt;D50&lt;/sub&gt;, Gemcitabine at 50% baseline size (gram)</td>
<td>3.2</td>
<td>136</td>
<td>(5.5, 16)</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2, KPD Effect half-life (week)</td>
<td>2.5</td>
<td>29</td>
<td>(0.61, 12.8)</td>
</tr>
</tbody>
</table>

* = Scaled to baseline tumour size
BSV = Between Subject Variability
95%CI = Empirical confidence interval from 1000 bootstraps

Residual Error

Proportional error: 12%
### Slide 19

**Why Stop Treatment?**

- Tumour size is still getting smaller when protocol dosing stops.

![Graph showing effective amount of drug (g) vs tumour size (cm) over weeks.](Image)

### Slide 20

**Which Exposure Metric?**

- No better fit with intracellular gemcitabine metabolite (or dfdU) compared to gemcitabine AUC.
- No better fit with individual predicted AUC compared with individual dose of gemcitabine.
- Dose is the simplest exposure metric.

### Slide 21

**What Was Learned About Exposure-Response?**

- No evidence that differences in exposure time course \([C(t)]\) can influence tumour response.
- No evidence that intracellular metabolite is better than dose as a predictor of tumour response.
- Unable to learn about influence of dose and duration of infusion.

*Didn't learn very much!*

*Uninformative design*

*“Absence of evidence is not evidence of absence”*
How Can Tumour Response be Used?

- Can quantitate individual sensitivity (ED50) and time course (drug effect and tumour ‘half-lives’)
- Complements toxicity based models e.g. Friberg myelosuppression model (optimal dosing?)
- Link to survival probability (Claret et al 2009, Wang et al 2009)

FDA Model Linking Tumour Size with Survival


Wang (FDA) Tumour Size Model

"A model with mixed exponential-decay (shrinkage) and linear-growth (progression) components described the time course of tumor change

$$TS_i(t) = BASE_i \cdot e^{-SR_i \cdot t} + PR_i \cdot t$$

where $TS_i(t)$ is the tumor size at time $t$ for the $i$th individual, $BASE$ is the baseline tumor size, $SR_i$ is the exponential tumor shrinkage rate constant, and $PR_i$ is the linear tumor progression rate."

Empirical model
No dose or exposure information used

Claret Tumour Size Model

The model is described by the differential equation below:

$$\frac{dy(t)}{dt} = K_0 \gamma(t) - K_D(t) \cdot \text{Exposure}(t) \gamma(t) \quad y(0) = y_0$$

with

$$K_D(t) = K_D \cdot e^{-\lambda t}$$

in which $\gamma(t)$ is the tumour size at time $t$, $y_0$ is the baseline tumour size, $K_0$ is the tumour growth rate, $K_D(t)$ is the drug-constant cell kill rate that decreases exponentially with time (according to $\lambda$) from an initial value of $K_D$ to account for the progressive development of resistance. Exposure(t) is the drug exposure at time $t$. Because no pharmacokinetic data were available, the daily dose was used as a metric for exposure to drive drug effect.

*DailyDose(t)*$^*_{exp(-\lambda*t)}$ 'resistance' function cannot be distinguished from a KPD model with drug elimination.


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Tumour Size and Survival

Wang/Claret

- ECOG (0/1), baseline tumor size (centered at 8.5 cm) as covariates
- Tumor size predictors (early biomarker)
  - Individual predicted tumor size percent reduction at 4, 6 or 8 weeks relative to baseline ($\text{TPR}_{\text{max}}$)
- Model development
  - Parametric survival model (log-normal)
  $$\log(T) = \alpha_0 + \alpha_1 \cdot \text{ECOG} + \alpha_2 \cdot (\text{Baseline} - 8.5) + \alpha_3 \cdot \text{TPR}_{\text{max}} + \epsilon$$

Linear Shrinkage Rate over 8 weeks


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Tumour Size Predictions

Model Fits for Individuals


Tumour Size Improves Prediction of Survival

Contribution of TPR_{wk8}
A1 Model Predicts C1


Which Patient Will Survive Longer?

Wang et al. use a single 8 week estimate of tumor progression rate. These patients have the same 8 week tumour size but different response time course

Perhaps survival models should include full time course of tumour size?

Can Anti-Cancer Drugs Be Developed More Efficiently?

Traditional Oncology
- Open Phase 2 trials
  - Biased outcome
- Dose
  - Pick the biggest dose
- Outcome
  - Categorical (RECIST)
- Dosing Regimen
  - '3 week cycle x 6'
  - BSA dosing (discredited theory)

Clinical Pharmacology
- Blinded Phase 2 trials
  - Unbiased
- Dose
  - Designed to learn Dose Response
- Outcome
  - Continuous biomarker (Tumour size)
- Dosing Regimen
  - Drug and patient individualized
  - Guided by PKPD (Evans et al. 1998)

Way to go!