A longitudinal tumor growth inhibition model for low-grade glioma

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Introduction

- Rate of successful development in oncology: 5%
- For compounds entering phase III: only 40%
- FDA recommends the use of quantitative methods for leveraging knowledge from clinical data
- **Objective**: to be able to predict long-term clinical outcome from early clinical evaluation
- **Means**: through modeling time-course of tumor shrinkage (tumor-growth inhibition model)
Existing models / relevance

- Wang et al. CPT 2009 for NSCLC
  - Link time of death to change in tumor size observed 8 weeks after therapy starts, thus providing a method for early screening of candidate drugs

- Claret et al. JCO 2010 for CRC
  - Predict survival in phase III trial based on the modeling of tumor size dynamic in phase II
Low grade gliomas

- WHO grade II gliomas (LGG) are diffusely infiltrative brain tumors affecting young adults
- Tumor grows slowly: 1-2 mm/year (≈10 times less than high grade gliomas)
- Patients mainly asymptomatic for years
- Tumor size is monitored with periodic MRIs
- Treatment starts when tumor size gets too high
Treatments

• None of them is curative

• Surgery, radiotherapy and chemotherapy (Temodal®, and PCV)

• PCV chemotherapy induce prolonged response:
  - Tumor size can decrease in patients for a prolonged period (> 2 years) after treatment stops

• Could the characterization of this prolonged response help to suggest improvements of the therapeutic protocol?
Data description

• Tumor size from 21 patients

• PCV treatment protocol: a maximum of 6 cycles (high toxicity) with a 6-weeks interval
  - **Procarbazine** (alkylating agent - phase nonspecific): 60 mg/m² on days 8-21
  - **Lomustine** (alkylating agent - phase nonspecific): 110 mg/m² on day 1
  - **Vincristine** (S-phase specific): 1.4 mg/m², maximum 2 mg/m² on day 8 and 29
Tumor size measurements

- Printed images were available
- Tumor volumes were estimated manually using three diameters \((D_1 \times D_2 \times D_3/2)\)
- Tumor volume were converted into a mean tumor diameter \(MTD (2 \times V^{1/3})\)
- Conventional method to assess LGG growth dynamic
21 low-grade glioma patients treated with PCV chemotherapy (Procarbazine, CCNU, Vincristine)
Time 0 corresponds to the time of treatment.

Treatment starts at Time 0 and ends at Time 60.

Max. tumor shrinkage occurs at approximately Time 20.

Diagnosis is indicated by the image labeled A.
Time 0 corresponds to the time of treatment

Time (months)

MTD (mm)

Diagnosis

Treatment starts

Max. tumor shrinkage

Treatment ends
Underlying hypothesis

- LGG is composed by proliferative and quiescent cell tissues
- Cytotoxics induce direct kill of proliferating cells
- Quiescent cells that have sustained DNA damages due to treatment subsequently die when re-entering the cell cycle
Modeling treatment

• Treatment is represented as a whole by a unique variable (C), virtual drug concentration encompassing the three agents

• We assume this concentration to exponentially decay through the parameter KDE that we estimate

• At the time of treatments (t = Ttreat), we set C = 1 (arbitrary unit)
PROLIFERATIVE TISSUE

Lesions repair?

\( \delta_{QP} \)

\( k_{QPP} \)

\( \lambda_p \)

QUIESCENT TISSUE

\( Q_p \)

Damaged quiescent tissue

\( Q \)

Undamaged quiescent tissue

CONCENTRATION

\( \gamma \)

KDE

DOSE

DEATH
Mathematical equations

\[
\frac{dC}{dt} = -KDE \times C
\]

\[
\frac{dP}{dt} = \lambda_p \times P \left(1 - \frac{P^*}{K}\right) + k_{QpP} \times Q_p - k_{PQ} \times P - \gamma_p \times C \times P
\]

\[
\frac{dQ}{dt} = k_{PQ}P - \gamma_Q \times C \times Q
\]

\[
\frac{dQ_P}{dt} = \gamma_Q \times C \times Q - k_{QPP}Q_P - \delta_{Qp} \times Q_P
\]

\[P^* = P + Q + Q_P\]
Parameters

- System of 4 compartments written as ordinary differential equations
- 6 parameters and 2 initial conditions \((P_0 \text{ and } Q_0)\)
- \(\lambda_P\) (growth rate) and \(k_{PQ}\) (quiescence rate) only regulates tumor growth in the absence of treatment
Statistical framework

- The model was developed within a mixed-effect (population) context where structural parameters are associated with inter-individual variability.
  - 8 fixed parameters and 7 inter-individual variability parameters.
- The software Monolix was used to estimate parameters.
## Parameter estimates PCV

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Description</th>
<th>Mean value (SE%)</th>
<th>IIV (SE%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_0$ (mm)</td>
<td>Baseline on $P$</td>
<td>7.13 (25)</td>
<td>94% (23)</td>
</tr>
<tr>
<td>$Q_0$ (mm)</td>
<td>Baseline on $Q$</td>
<td>41.2 (7)</td>
<td>54% (10)</td>
</tr>
<tr>
<td>$\lambda_P$ (month$^{-1}$)</td>
<td>Growth rate</td>
<td>0.121 (16)</td>
<td>72% (9)</td>
</tr>
<tr>
<td>$k_{PQ}$ (month$^{-1}$)</td>
<td>Quiescence rate</td>
<td>0.030 (21)</td>
<td>76% (12)</td>
</tr>
<tr>
<td>$k_{QP}$ (month$^{-1}$)</td>
<td>Feedback to proliferation</td>
<td>0.003 (35)</td>
<td>97% (31)</td>
</tr>
<tr>
<td>$\delta_{Q^*}$ (month$^{-1}$)</td>
<td>Elimination rate</td>
<td>0.009 (21)</td>
<td>75% (12)</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Treatment efficacy</td>
<td>0.729 (37)</td>
<td>115% (9)</td>
</tr>
<tr>
<td>KDE (month$^{-1}$)</td>
<td>Drug elimination rate</td>
<td>0.240 (33)</td>
<td>70% (-)</td>
</tr>
</tbody>
</table>
Staining MIB-1 antibody for Ki-67

Heester et al. Journal of Neurology 1999

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>MIB1 INDEX</th>
<th>Observed (n=24)</th>
<th>Predicted (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytoma</td>
<td>AG</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Anaplastic A.</td>
<td>176</td>
<td>176</td>
</tr>
<tr>
<td></td>
<td>Oligod. + OA</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Oligodendroglialmas</td>
<td></td>
<td>15% (SD=10%)</td>
<td>14% (SD=10%)</td>
</tr>
</tbody>
</table>
Additional datasets

- Radiotherapy (n=25 patients) - Salpêtrière hospital
- Temozolomide (TMZ) chemotherapy: (n=24 patients randomly selected) - Salpêtrière hospital
Radiotherapy

Mean tumor diameter (mm) vs. Time (months) graph

- X-axis: Time (months)
- Y-axis: Mean tumor diameter (mm)
\( \varepsilon \)-shrinkage: 14\%
Temozolomide (TMZ) chemotherapy
MPIs

NPDEs

ε-shrinkage: 7%
## Parameter consistency

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>PCV</th>
<th>RT</th>
<th>TMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor baseline</td>
<td>48.3 mm</td>
<td>44.2 mm</td>
<td>43.2 mm</td>
</tr>
<tr>
<td>Basic doubling time for the proliferative tissue</td>
<td>8.3 months</td>
<td>7.3 months</td>
<td>8.8 months</td>
</tr>
<tr>
<td>Ratio proliferation rate versus quiescence rate</td>
<td>4.0</td>
<td>5.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Ratio death rate versus proliferation rate for DNA-damaged quiescent tissue</td>
<td>3.0</td>
<td>No feedback to proliferation</td>
<td>4.2</td>
</tr>
</tbody>
</table>
Prolonged response

Fraction of proliferative tissue

PATIENT 3

MTD

Time

First PCV cycle

Last PCV cycle

P (mm)

0 10 20 30 40 50 60 70 80 90 100

Time (months)

PATIENT 3

Fraction of proliferative tissue

MTD

Time

First PCV cycle

Last PCV cycle

P (mm)
Lengthening time interval

1 cycle every 6 weeks → 1 cycle every 9 months

PATIENT 3

Lengthening time interval

1 cycle every 6 weeks → 1 cycle every 9 months

PATIENT 3
<table>
<thead>
<tr>
<th></th>
<th>PCV 6 weeks</th>
<th></th>
<th>PCV 9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTD shrink</td>
<td>-34%</td>
<td>MTD shrink</td>
<td>-40%</td>
</tr>
<tr>
<td>Prolonged</td>
<td>36 months</td>
<td>Prolonged</td>
<td>64 months</td>
</tr>
<tr>
<td>response</td>
<td></td>
<td>response</td>
<td></td>
</tr>
</tbody>
</table>
Clinical translation

- Give only 3 cycles according to the classical protocol (every 2 months) and then monitor the tumor size for 9 months with periodic MRI
  - If the tumor resumes its growth (or remain stable) within the 9 months, start again treatment following the classical protocol
  - If the tumor size continues decreasing after 9 months, increase the treatment interval
New patient

Give 3 cycles with 6-weeks interval

Stop treating and monitor

MTD still decrease?

NO

max. 9 months

max. \( T_0 + 15 \) months

YES

Give 3 cycles with 9-months interval

\( T_0 + 33 \) months
Conclusions

• We propose a semi-mechanistic TGI model for low-grade glioma patients

• Parameters can be classified into:
  - system-specific parameters
  - treatment related parameters

• Consistency of system-specific parameters across different treatments including radiotherapy

• Future work includes link with long-term clinical outcome