OPTIMIZATION OF CHEMOTHERAPY DELIVERY PROTOCOLS, TO TREAT LOW-GRADE GLIOMA PATIENTS
CONTEXT

- Low-grade glioma: brain tumor with slow and continuous growth
- Different treatments

Surgery  Radiotherapy  Chemotherapy

PCV  TMZ
Prolonged response with PCV[1]

Prolonged response with PCV[1]

How could we modify PCV delivery protocol?

RESISTANCE TO TMZ

Patient 8

Patient 14

Patient 15

Patient 44

Patient 47

Patient 48

MTD (mm)

Time (months)
RESISTANCE TO TMZ

How could we model the emergence of resistance to TMZ?

How could we optimize treatment duration and TMZ delivery protocol?
OBJECTIVES

To use mathematical modeling to

- Propose modifications of therapeutic protocols on a population level
- Optimize the treatment delivery on an individual level
\[
\frac{dC}{dt} = -KDE \times C
\]

\[
\frac{dP}{dt} = \lambda_P P \left(1 - \frac{P^*}{K}\right) - k_{PQ} P - \gamma C \times KDE \times P + k_{Qp} P Q_p
\]

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

\[
\frac{dQ_p}{dt} = \gamma C \times KDE \times Q - k_{Qp} P Q_p - \delta Q_Q p
\]

\[
P^* = P + Q + Q_p
\]

MODIFICATION OF PCV DELIVERY PROTOCOL
INDIVIDUAL FITS

Patient 2

Patient 3

- Tumor
- Quiescent tissue
- Proliferative tissue
- Treatment
Modification of PCV administration for a population\[^3\]

- Modification of therapeutic protocol:
  \[
  \frac{dC}{dt} = -KDE \times C
  \]

- Constraints for the modifications:
  - 6 PCV cycles
  - Same time interval between cycles

- Aims:
  - To prolong tumor response duration
  - To avoid tumor progression between PCV cycles

- Simulation of 1000 virtual LGG patients

\[^3\] Mazzocco, P. et al., 2015. Increasing the time interval between PCV chemotherapy cycles as a strategy to improve duration of response in low-grade gliomas: results from a model-based clinical trial simulation, submitted to *Computational and Mathematical Methods in Medicine*. 
Simulations with modified protocol

Individual fits with standard protocol
Individual fits with standard protocol

Simulations with modified protocol

Proliferative tissue (%)

Time (months)
Population optimization

![Graph showing the proportion of patients in response over time](attachment:image.png)

- Y-axis: Proportion of patients in response
- X-axis: Time (years)

The graph illustrates the decrease in the proportion of patients in response over time, with two distinct curves indicating different patient responses over the years.
Increasing the interval between PCV cycles up to 6 months allows to significantly prolong tumor decrease duration.
MODELING TUMOR RESISTANCE TO TMZ, AND OPTIMIZATION OF TREATMENT DELIVERY
Resistance modeling

- Resistance to chemotherapy: one of the main reasons of treatment failure
- Due to random mutations and/or caused by the treatment itself[4]
- Usually described with $\gamma \times \exp(-res.\ t)$[5]
- Existence of models distinguishing between sensitive and resistant tumor cells[6]

Resistance modeling

- Use of stochastic discrete models to describe the emergence of resistance[7]

- Issues with simulations and parameter estimations

- Possibility to use stochastic differential equations (SDE) (continuous time), but issues with parameter estimations

- ODE model: limit of SDE model with large initial population

DATA[8]

- 77 patients treated with TMZ
- 952 tumor size observations in total
- Administration protocol: 200mg/m²/d, from day 1 to day 5, every 28 days
- 18 cycles of TMZ in median (minimum 2, maximum 24)
- 34 patients experienced tumor progression during treatment
- 1p/19q co-deletion, p53 mutation and IDH mutation statuses available

INDIVIDUAL PROFILES

Tumor progression when treatment stops

Prolonged response

Failure of therapy: resistance to treatment
PK-PD Model

\[
\frac{dC_1}{dt} = -k_a C_1 + Adm(t)
\]

\[
\frac{dC_2}{dt} = k_a C_1 - \frac{CL}{Vd} C_2
\]

\[
C(t) = \frac{C_2(t)}{Vd} 
\]

\[
AUC(t) = \int_{t_0}^{t} C(x)dx
\]

\[
\begin{align*}
\frac{dC_1}{dt} &= -k_a C_1 + Adm(t) \\
\frac{dC_2}{dt} &= k_a C_1 - \frac{CL}{Vd} C_2 \\
C(t) &= \frac{C_2(t)}{Vd} \\
AUC(t) &= \int_{t_0}^{t} C(x)dx \\
\frac{dS}{dt} &= \lambda_S S \left(1 - \frac{T}{100}\right) - \gamma_{SD} C(t)S \\
\frac{dR}{dt} &= \lambda_R R \left(1 - \frac{T}{100}\right) + \gamma_{DR} AUC(t) D \\
\frac{dD}{dt} &= \gamma_{SD} C(t)S - \mu_D D - \gamma_{DR} AUC(t) D \\
T &= S + R + D \\
S_0 &= Y_0 \times K, \quad R_0 = Y_0 (1 - K), \quad D_0 = 0
\end{align*}
\]
INDIVIDUAL FITS

**Low proliferation rate for cells S**

ID35

**Low proliferation rate for cells S but capacity to repair lesions**

ID49

**High proliferation rate for cells S and large capacity to repair lesions**

ID44

Legend:
- Blue: Tumor
- Red: Sensitive tissue
- Black: Damaged tissue
- Pink: Resistant tissue
- Gray: Treatment
INDIVIDUAL OPTIMIZATION - METHOD

- Optimization of TMZ administration protocol, on an individual level with CMA-ES algorithm

- Constraints:
  - 5 TMZ administrations per cycle
  - Same time interval between cycles (interval > 5 days)
  - Dose \( \leq 200 \text{mg/m}^2/\text{d} \)

- Test of 3 different numbers of TMZ cycles per patient

- Aims:
  - To prolong tumor decrease duration (TTG)
  - To minimize tumor size (MTS)

- Optimization criteria:
  \[ \frac{TTG_{\text{optim}}}{TTG_{\text{standard}}} + \frac{MTS_{\text{standard}}}{MTS_{\text{optim}}} \]
Simulation of the optimized protocol with stochastic differential equations (SDE)

Description of a random phenomenon (cell mutations) with a stochastic approach

Robustness evaluation of model and method

Stochastic equations, on resistant process, for resistant and damaged tissues:

\[
\frac{dR}{dt} = \lambda_R R \left(1 - \frac{T}{100}\right) + (\gamma_{DR} + \sigma_{DR} \times \varepsilon) AUC(t)D
\]

\[
\frac{dD}{dt} = \gamma_{SD} C(t)S - \mu_D D - (\gamma_{DR} + \sigma_{DR} \times \varepsilon) AUC(t)D
\]

where \( \varepsilon \sim \mathcal{N}(0,1) \)
Patient 35 – TMZ optimization

Standard protocol: 10 cycles, every 28 days, 200mg/m²/d

Optimized protocol 1: 10 cycles, every 150 days (5 months), 200mg/m²/d

Optimized protocol 2: 15 cycles, every 130 days (4.3 months), 200mg/m²/d

Optimized protocol 3: 20 cycles, every 115 days (3.8 months), 200mg/m²/d
Patient 35 – Evaluation of Optimized Protocol

**Tumor size dynamics**

**Resistant cells dynamics**

- Standard protocol
- Optimized protocol

**Time to tumor growth**

**Minimal tumor size**

- Time (months)
- MTD (mm)
**Patient 49 – TMZ Optimization**

Standard protocol: 12 cycles, every 28 days, 200mg/m²/d

Optimized protocol 1: 12 cycles, every 100 days (3.3 months), 200mg/m²/d

Optimized protocol 2: 17 cycles, every 65 days (2.2 months), 200mg/m²/d

Optimized protocol 3: 22 cycles, every 45 days (1.5 months), 200mg/m²/d
Patient 49 – Evaluation of Optimized Protocol

Tumor size dynamics

Resistant cells dynamics

- Standard protocol
- Optimized protocol

Time to tumor growth

Minimal tumor size

MTD (mm)
Patient 44 – TMZ Optimization

Standard protocol: 20 cycles, every 28 days, 200mg/m²/d

Optimized protocol 1: 20 cycles, every 72 days (2.4 months), 120mg/m²/d

Optimized protocol 2: 10 cycles, every 135 days (4.5 months), 200mg/m²/d

Optimized protocol 3: 15 cycles every 55 days (1.8 months), 90mg/m²/d
Patient 44 – Evaluation of Optimized Protocol

Tumor size dynamics

Resistant cells dynamics

Time to tumor growth

Minimal tumor size

MTD (mm)

Cell density (mm)

Time (months)

Time (months)

MTD (mm)

0

10

20

30

0

25

30

35

0

0.01

0.02

0.03

0.04

0.05

0.06

0.07

0.08

0.09

0.1

0

10

20

30

40

45

50

-40

-20

0

20

40

-40

-20

0

20

40

-40

-20

0

20

40

-40

-20

0

20

40

Standard protocol

Optimized protocol
CONCLUSION

- Study of LGG patients treated with chemotherapy (PCV and TMZ)
- Population model to describe tumor dynamics
- Modification of PCV therapeutic protocol
- Optimization of TMZ delivery protocol on an individual level

Limits

- Few patients included in the analysis, in particular with covariates
- No available PK data
WHAT CAN WE DO?

- Optimization of TMZ delivery protocol for a population

First group of patients, treated with the standard protocol

Population model, with covariates

Second group of patients, treated with the optimized protocol

Optimization of TMZ delivery protocol and evaluation with SDEs
What can we do?

- Optimization of TMZ delivery protocol for a population
- Prediction and adjustment of TMZ delivery protocol for a patient

3 months of treatment with the standard protocol

If optimized protocol does not prolong tumor decrease, treatment stop

Estimation of MAP parameters with these observations

Optimization of TMZ delivery protocol for the next 4 cycles and evaluation with SDEs

If optimized protocol does prolong tumor decrease, administration of 4 more cycles
THANK YOU FOR YOUR ATTENTION