Mathematical model suggests a way to assess LGG malignancy

M.U. Bogdańska, M. Bodnar, J. Belmonte-Beitia,
M. Murek, P. Schucht, J. Beck, V. M. Pérez-García

Biological motivation

Low grade gliomas (LGGs) - slowly growing, incurable brain tumours. They occur in young and otherwise healthy patients; life-prolonging treatment should not come at the cost of compromising the quality of life. Management decisions, whether and when should a patient receive resection, radio- or chemotherapy, are not fully standardized. Due to long patients' survival, clinical trials on LGGs require about ten years to test a single hypothesis.

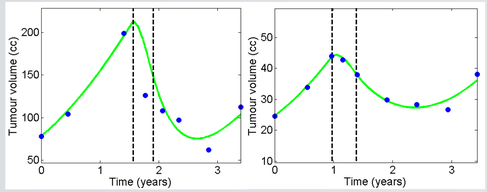
Chemotherapy for LGGs

Temozolomide (TMZ) - a drug of choice for clinicians, effective for both previously irradiated and unrradiated LGGs. TMZ-induced damage provoke mitotic catastrophe causing cell death long after the end of therapy as observed in clinics [1,2]. Proper timing and fractionation of TMZ treatment - unknown.

Questions

How can we model chemotherapy for LGGs?
Could we estimate their aggressiveness and response to standard therapies causing minimal cytotoxicity?

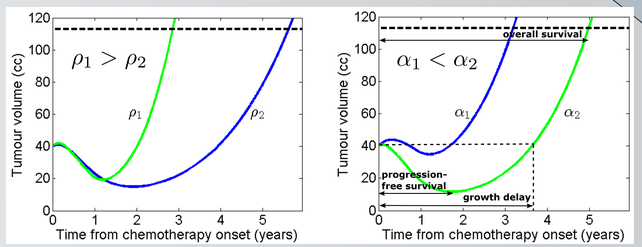
Model fitting to patients' data



Tumour volume evolution for patients treated with TMZ (treatment duration marked with vertical dashed lines). We fit ρ using volumes before chemotherapy onset, based on following data we estimate α and k. Method: weighted least squares. (left) Patient treated with 4 TMZ cycles, ρ = 0.002416/day, k = 0.2722, α = 1.387798ml/µg/day. (right) Patient treated with 5 TMZ cycles, ρ = 0.001761/day, k = 0.555867, α = 0.971918ml/µg/day.

Tumour response dependence on main prameters

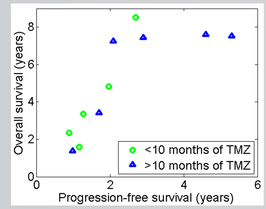
Tumour volume evolution after 12 standard chemotherapy cycles with k=0.5. The horizontal dotted lines correspond to tumour sizes equal to the fatal tumour burden (critical size causing death).



Progression-free survival (PFS) - time until the onset of tumour regrowth after therapy
growth delay - time for which the tumour volume after the therapy equals the initial one
overall survival - time till death

faster response → **worse prognosis**

Progression-free survival and overall survival of LGGs patients treated with temozolomide.



$$\begin{aligned}\frac{\mathrm{d}P}{\mathrm{d}t} &= \rho P\left(1-\frac{P+D}{K}\right)-\alpha PC,\\ \frac{\mathrm{d}D}{\mathrm{d}t} &= -\frac{\rho}{k}D\left(1-\frac{P+D}{K}\right)+\alpha PC,\\ \frac{\mathrm{d}C}{\mathrm{d}t} &= -\lambda C\end{aligned}$$

$P(t)$ - functionally alive glioma cells
$D(t)$ - cells irreversibly damaged by chemotherapy
$C(t)$ - drug concentration in brain
Chemotherapy consists of a sequence of doses $d_1, d_2, \ldots, d_n$ given at times $t_1 < t_2 < \ldots < t_n$.

$$P(t_1) = P_1, \quad D(t_1) = 0$$
$$P(t_j) = P(t_j^-), \quad D(t_j) = D(t_j^-),$$
$$C(t_j) = C(t_j^-) + C_j \quad \text{for } j = 1, \ldots, n$$

Heuristic model

LGGs' net cell division is given by logistic term with parameter ρ.

TMZ administration is treated as a discontinuous change in its concentration. Then it decays exponentially owing to drug clearance.

The number of cells damaged by TMZ in a time unit is proportional to concentration of drug and number of proliferating tumour cells with rate α.

Glioma cells irreversibly damaged by TMZ try to enter mitosis with the same probability as those active and die after such k attempts, resulting in "negative" proliferation with coefficient $-\rho/k$.

Parameters' values

carrying capacity K - from max. gliomas' diameter (~10 cm) [2]

rate of TMZ decay λ - from TMZ half-life clearance [3]

proliferation rate ρ - usually $(1-5)\cdot 10^{-3}$/day (its inverse = typical cell doubling time) [4]

Patients' data

volumetric data of LGGs' patients treated with TMZ at Bern University Hospital in 1990-2013.

Standard TMZ fractionation

cycles of 28 days:
- 5 days of dosing
- 23 days of break

dose: 150mg/day/m^2 of patient body surface

Analytical estimates of tumour response

Chemotherapy will be administered in cycles of T days with p doses of drug given every r days. We rescale model taking

$$x = P/K,\ y = D/K,\ z = \alpha C/\rho,\ s = \rho t,\ \mu = \lambda/\rho.$$

Initial conditions are of a form:

$$x(0) = x_0 = P_0/K,\ y(0) = 0,\ z(0) = z_0 = \alpha C_0/\rho$$

The rescaled dose z_0 is given in time moments $s_1 = 0, s_2, \ldots, s_n$.

We find progression-free survival as a time of maximal tumour mass reduction, i.e.

$$P(t_{\mathrm{PFS}}) + D(t_{\mathrm{PFS}}) = \min_{t \geq t_n} \{P(t) + D(t)\}.$$

In terms of re-scaled model we aim to estimate

$$x(s_{\mathrm{PFS}}) + y(s_{\mathrm{PFS}}) = \min_{s \geq s_n} \{x(s) + y(s)\}.$$

We have $x(s_{\mathrm{PFS}}) = \frac{1}{k} y(s_{\mathrm{PFS}})$ and $s_{\mathrm{PFS}} = \rho \cdot t_{\mathrm{PFS}}$.

Assumptions

1. As therapy cause a tumour mass reduction, we can assume that the total tumour mass at the time around PFS is substantially smaller than the carrying capacity

$$\begin{aligned}\frac{\mathrm{d}x}{\mathrm{d}s} &= x - xz\\ \frac{\mathrm{d}y}{\mathrm{d}s} &= -\frac{1}{k}y + xz\\ \frac{\mathrm{d}z}{\mathrm{d}s} &= -\mu z\end{aligned}$$

2. Each dose is cleared in one day [3]

$$z(s) \approx \begin{cases} z_0 \mathrm{e}^{-\mu(s-s_j)} & s \in (s_j, s_j+\rho) \\ 0 & \text{for other } s \end{cases}$$

3. $$\mathrm{e}^{-\mu t} - 1 \approx \begin{cases} -\mu t & 0 \leq t < \frac{1}{\mu} \\ -1 & t \geq \frac{1}{\mu} \end{cases}$$

Denoting $w(s) = \int_0^s z(t)\mathrm{d}t,\ w_0 = w(\rho) = \frac{z_0}{\mu}\left(1-\mathrm{e}^{-\mu\rho}\right)$ we obtain for $s > s_n + \rho$

$$x(s) = x_0 \mathrm{e}^{s - nw_0}, \quad y(s) = \int_0^s \mathrm{e}^{-\frac{s-t}{k}} x(t) z(t) \mathrm{d}t$$

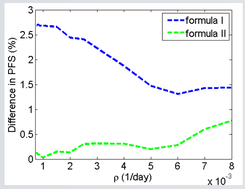
$$k\mathrm{e}^{(1+1/k)s_{\mathrm{PFS}} - nw_0} = \int_0^{s_{\mathrm{PFS}}} \mathrm{e}^{(1+1/k)t - w(t)} z(t) \mathrm{d}t$$

$$s_{\mathrm{PFS}} = \frac{1}{\tilde{k}}\left[nw_0 + \ln\left(\frac{1}{k}\int_0^{s_{\mathrm{PFS}}} \mathrm{e}^{\tilde{k}t - w(t)} z(t) \mathrm{d}t\right)\right] \quad \text{with } \tilde{k} = 1 + 1/k$$

$$z_0\left(\sum_{j=1}^{n} \mathrm{e}^{-(j-1)w_0 + \tilde{k}s_j}\right) \int_0^{\rho} \mathrm{e}^{(\tilde{k}-\mu)t + \frac{z_0}{\mu}\left(\mathrm{e}^{-\mu t} - 1\right)} \mathrm{d}t$$

$$t_{\mathrm{PFS}} = \frac{nw_0}{k\rho} + \frac{1}{k\rho}\ln\left\{z_0 \mathrm{e}^{\frac{\tilde{k}-\mu-z_0}{\mu} - \tilde{k} + \mu + \left(\tilde{k}-\mu-z_0\right)\mathrm{e}^{\left(\tilde{k}-\mu\right)\rho - \frac{z_0}{\mu}}}\right\} + \frac{1}{k\rho}\ln\left\{\frac{z_0\left(1-\mathrm{e}^{\left(-pw_0+\tilde{k}\rho T\right)\frac{n}{p}}\right)\left(1-\mathrm{e}^{\left(-w_0+\tilde{k}\rho r\right)p}\right)}{\tilde{k}\left(1-\mathrm{e}^{-pw_0+\tilde{k}\rho T}\right)\left(1-\mathrm{e}^{-w_0+\tilde{k}\rho r}\right)\left(\tilde{k}-\mu-z_0\right)\left(\tilde{k}-\mu\right)}\right\} \quad \text{I}$$

$$t_{\mathrm{PFS}} = \frac{nw_0}{k\rho} + \frac{1}{k\rho}\ln\left\{\frac{z_0 p}{\mu\tilde{k}}\left(1-\mathrm{e}^{-pw_0+\tilde{k}\rho T}\right)\left(1-\mathrm{e}^{-nw_0+\tilde{k}\rho T\frac{n}{p}}\right)\right\} \quad \text{II}$$



Relative difference between progression-free survival calculated from simulations and estimated formulas.

Clinical implications

Short progression-free survival correlates with a poorer outcome.

Idea: use chemotherapy to probe tumour, providing estimates of tumour-specic parameters.

Tumour which attains its minimal volume soon after short course of TMZ treatment (has shorter PFS) may be more aggressive $\Rightarrow$ TMZ treatment has to be finished soon, other therapeutical options should be considered.

Future research

- verify hypothesis on larger data set
- propose suitable "probing procedure"
- optimize treatment schedules giving the longest PFS possible while maintaining the toxicity in acceptable levels
- include more biological details (acquiring chemoresistance, stem cells)

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The design of this poster is based on work of Felix Breuer.