A Tumor Growth Inhibition Model For Low-Grade Glioma Treated With Chemotherapy or Radiotherapy

Benjamin Ribba1*, Gentian Kaloshi2, Mathieu Peyre3, Damien Ricard4, Vincent Calvez1, Michel Tod5,6, Branka Čajavec-Bernard1, Ahmed Idbaih2, Dimitri Psimaras2, Linda Dainese7, Johan Pallud8, Stéphanie Cartalat-Carel3, Jean-Yves Delattre2, Jérôme Honnorat3,6,9, Emmanuel Grenier1, François Ducray3,6,9

1 - INRIA, Project-team NUMED, Ecole Normale Supérieure de Lyon, 46 allée d’Italie, 69007 Lyon Cedex 07, France.
2 - AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Service de Neurologie Mazarin ; INSERM, U975, Centre de Recherche de l’Institut du Cerveau et de la Moelle ; Université Pierre & Marie Curie Paris VI, Faculté de médecine Pitié-Salpêtrière, CNRS UMR 7225 and UMR-S975, Paris, France
3 - Hospices Civils de Lyon, Hôpital Neurologique, Neuro-oncologie, Lyon, 69003 France
4 - Hôpital d’Instruction des Armées du Val-de-Grâce, Paris, 75005 France
5 –EA3738 CTO, Faculté de Médecine Lyon-Sud, Oullins, F-69600, France ; Pharmacie, Hôpital de la Croix Rousse, Hospices civils de Lyon, 69004 Lyon, France
6 – Université de Lyon, Claude Bernard Lyon 1, Lyon, F-69003, France
7 – Service de Neupathologie, Hôpital de la Salpêtrière, 47 boulevard de l'Hôpital, Paris, France
8 - Service de Neurochirurgie, Centre Hospitalier Sainte-Anne, Paris, 75014 France, University Paris Descartes
9 - Lyon Neuroscience Research Center INSERM U1028/CNRS UMR 5292, Lyon, France

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* Corresponding author: Benjamin Ribba; benjamin.ribba@inria.fr; Tel:+33 4 76 61 52 00; Fax: +33 4 76 61 52 52
Translational relevance

In this work, we propose a model of tumor growth inhibition that successfully describes the time course of tumor size (measured as mean tumor diameter) in patients with low-grade glioma (LGG). We analyze mean tumor diameter dynamics in patients treated with three different forms of first-line therapy—chemotherapy (temozolomide or PCV (procarbazine, CCNU, vincristine)) or radiotherapy—and show that model performance and parameter estimates are consistent across treatment modalities. This model might constitute a rational tool to predict treatment efficacy and to optimize treatment schedules in LGG patients.
Abstract

Purpose: To develop a tumor growth inhibition model for adult diffuse low-grade gliomas (LGGs) able to describe tumor size evolution in patients treated with chemotherapy or radiotherapy.

Experimental design: Using longitudinal mean tumor diameter (MTD) data from 21 patients treated with first-line PCV chemotherapy, we formulated a model consisting of a system of differential equations, incorporating tumor-specific and treatment-related parameters, that reflect the response of proliferative and quiescent tumor tissue to treatment. The model was then applied to the analysis of longitudinal tumor size data in 24 patients treated with first-line temozolomide chemotherapy and in 25 patients treated with first-line radiotherapy.

Results: The model successfully described the MTD dynamics of LGG before, during and after PCV chemotherapy. Using the same model structure, we were also able to successfully describe the MTD dynamics in LGG patients treated with temozolomide chemotherapy or radiotherapy. Tumor-specific parameters were found to be consistent across the three treatment modalities. The model is robust to sensitivity analysis, and preliminary results suggest that it can predict treatment response based on pre-treatment tumor size data.

Conclusions: Using MTD data, we propose a tumor growth inhibition model able to describe LGG tumor size evolution in patients treated with chemotherapy or radiotherapy. In the future, this model might be used to predict treatment efficacy in LGG patients and could constitute a rational tool to conceive more effective chemotherapy schedules.
Introduction

The use of existing clinical data to model tumors' dynamic response to antitumor treatments is a promising approach towards improving treatment efficacy and accelerating the development of antitumor drugs. Such strategies have been applied, for example, to predict and monitor chemotherapy-induced myelosuppression (1). In addition, tumor growth inhibition (TGI) models have successfully been developed to assess tumor size dynamics following cytotoxic treatment in non-small cell lung cancer (NSCLC) (2, 3). In colorectal cancer, a TGI model was able to use data on tumor dynamics from a phase II study to predict overall survival in a subsequent phase III trial (4).

Herein we rely on clinical data to develop a TGI model for adult diffuse low-grade gliomas (LGGs). LGGs are progressive brain tumors characterized radiologically by slow and continuous growth preceding anaplastic transformation (5, 6). Despite advancements in treatment methods in recent years, most LGGs remain incurable. LGG treatment approaches include surgery, radiotherapy, and chemotherapy with PCV (procarbazine, CCNU, vincristine) or temozolomide (TMZ) (6).

Our model aims to capture the growth kinetics of LGG after chemotherapy or radiotherapy, and ultimately to serve as a rational tool that might provide insight into means of optimizing LGG treatment.

In a previous study, we showed that after termination of PCV chemotherapy, LGGs frequently continue to decrease in volume despite chemotherapy no longer being administered (7, 8). One potential cause for this effect is delayed action of chemotherapy on quiescent tumor cells. This hypothesis is consistent with the cell-cycle non-specific mechanism of action of the alkylating agents (procarbazine and especially CCNU) used in the PCV regimen (9). On the basis of this hypothesis, herein we use longitudinal tumor size data from patients treated with first-line PCV chemotherapy to formulate a TGI model in which LGGs consist of proliferative and quiescent tumor tissues that respond differently to treatment. We successfully use the model to analyze tumor size dynamics not only in patients treated with PCV chemotherapy but also in patients treated with TMZ chemotherapy or radiotherapy, and we show that the non-treatment-related parameters of the model are consistent across the three therapeutic modalities.
Material and methods

Patients and data collection

We analyzed longitudinal tumor size measurements from LGG patients treated with first-line PCV chemotherapy (n = 21 patients), first-line TMZ chemotherapy (n = 24) or first-line radiotherapy (n = 25). These treatment methods represent the main LGG treatment modalities used in various institutions (PCV is used in Lyon (8); radiotherapy was used at the Salpêtrière Hospital in Paris until the 1990s and was subsequently replaced by TMZ (7)). We did not consider surgery as a first-line treatment.

Patients left the study upon anaplastic transformation (histologically proven or suspected when rapidly growing foci of enhanced contrast appeared on imaging) or when tumor progression led to a need for a different form of treatment. Treatment was given either just after LGG diagnosis or after a follow-up period lasting up to several years.

The measurements analyzed in the three studies are shown in Figure 1. Tumor size measurements were expressed as mean tumor diameters (MTDs) in mm and were estimated manually from printed MRI images in which maximal radiological abnormalities were visible (5):

\[
MTD = \left(2 V \right)^{\frac{1}{3}}, \text{where } V = \frac{D_1 \times D_2 \times D_3}{2}
\]

is the approximated tumor volume with \(D_1\), \(D_2\), and \(D_3\) referring to the three largest measured perpendicular diameters.

As shown in Figure 1, the typical MTD curve is characterized by four phases: a slow-growing phase before treatment onset, a decrease in MTD upon treatment initiation, a prolongation (from months to several years) of this decrease after treatment termination, and a late and final regrowth phase.

PCV chemotherapy. We used tumor size data from a previously published study of a series of 21 LGG patients treated with first-line PCV, representing a total of 254 measurements (median, 12 points per patient; min, 4; max, 22) (8). These patients (13 females and 8 males) had been treated at the Pierre Wertheimer Neurological Hospital and the Léon Bérard Cancer Center in Lyon between 1994 and 2005 (8). The baseline
MTD (MTD at treatment) was 69 mm on average (median, 62 mm; min, 41 mm; max, 87 mm). The PCV protocol consisted of up to 6 cycles of the following treatment, with intervals of 6 weeks between cycles: CCNU (110 mg/m²) administered on day 1, procarbazine (60 mg/m²) administered on days 8–21 and vincristine (1.4 mg/m², maximum 2 mg) administered on days 8 and 29. Median age at PCV onset was 47 years. Median duration of the observation period was 81 months. Medians of 3 observations before treatment and 12 observations after treatment were available for each patient. The histological subtypes were grade II oligodendroglioma (n = 15), grade II oligoastrocytoma (n = 4), and grade II astrocytoma (n = 2).

**TMZ chemotherapy.** Tumor size data from 24 patients treated with first-line TMZ chemotherapy were used, representing a total of 294 measurements (median, 11 measurements per patient; min, 5; max, 23). These patients (14 females and 10 males) had been treated at the Salpêtrière Hospital between 2000 and 2005 (7). The baseline MTD was 51 mm on average (median, 48 mm; min, 26 mm; max, 85 mm). Treatment consisted of up to 30 cycles of TMZ administration; in each cycle, TMZ was administered orally from days 1 through 5 at a dose of 150–200 mg/m²/day; administration was repeated every 28 days. Median age at TMZ onset was 45 years. Median duration of the observation period was 42 months. The median numbers of observations per patient were 3 and 8 before and after treatment onset, respectively. We used data for a limited number of patients (n = 24), randomly selected from a group of 120 patients for whom data were available (7). This allowed us to preserve homogeneity across the three treatment groups in terms of the number of subjects. However, the remaining 96 patients were used for external validation of the model. The histological subtypes were grade II oligodendroglioma (n = 20), grade II oligoastrocytoma (n = 3), and grade II astrocytoma (n = 1).

**Radiotherapy.** We measured the time course of the MTD of 25 patients treated with first-line radiotherapy; measurements were carried out specifically for this study. We obtained a total of 249 measurements (median, 9 measurements per patient; min, 5; max, 21). These patients (11 females and 14 males) had been treated at the Salpêtrière Hospital between 1990 and 2001. Baseline MTD was 49 mm on average (median, 48 mm; min, 24 mm; max, 82 mm). Radiotherapy was administered daily at a median
total dose of 54 Gy (min, 30 Gy; max, 60 Gy), with a median dose per fraction of 1.8 Gy. Median age at radiotherapy onset was 39 years. Median duration of the observation period was 65 months. Medians of 1 and 8 observations per patient were available before and after treatment, respectively. The histological subtypes were grade II oligodendroglioma \((n = 7)\), grade II oligoastrocytoma \((n = 6)\), and grade II astrocytoma \((n = 12)\).

**Modeling technique**

The tumor model we formulated belongs to the category of mixed-effects models (10). In this modeling technique, all individual data are analyzed simultaneously in order to provide information about the progression of each individual tumor. The modeling process comprises two steps. In the first step, a likelihood function is minimized to estimate the mean values of the model parameters as well as their inter-individual variability throughout the population. The resulting estimates are called “population parameters”. In the second step, we use information on the population parameters to estimate the best model parameters for each individual based on his or her individual dataset. These parameters are called “individual parameters”. The Monolix® software (Lixoft), based on the stochastic approximation of the expectation-maximization (SAEM) algorithm, was used to estimate the population and individual parameters (11). We evaluated the model according to goodness of fit, residual plots, and precision of parameter estimates as relative standard errors. We calculated the \(\varepsilon\)-shrinkage and \(\eta\)-shrinkage to analyze the degree of shrinkage of individual predictions towards the observations (12). \(\eta\)-shrinkage refers to shrinkage of the individual model parameters, and \(\varepsilon\)-shrinkage refers to residual error model parameters. In cases of low \(\varepsilon\)-shrinkage (<15%), individual predictions were considered to be reliable for model diagnostics. We also examined the normalized prediction distribution errors because this criterion is a powerful tool for detecting bias in model formulation with respect to available data (13). The prediction discrepancy of an observation is the percentile of that observation in the posterior distribution of the predicted MTD values, obtained by Monte-Carlo simulations of the population model. By construction, the normalized prediction distribution errors follow a normal distribution with mean 0 and variance equal to 1.

**Modeling strategy**
To develop the model, we used longitudinal tumor size data from the 21 patients treated with PCV chemotherapy (Figure 1). To select the best model from among multiple model structures, we used the objective function \( OBJ = -2 \times LLH \), where \( LLH \) is the log-likelihood value, and the Bayesian information criterion \( BIC = -2 \times LLH + \log (n)k \), where \( k \) is the total number of parameters and \( n \) is the number of subjects. Additional information on the strategy used for model selection and evaluation is presented in the supplementary data (“Model selection” section and Figure S1).

We chose to base the model development on the PCV dataset for two reasons. First, it seemed to us essential for our model to be able to describe the ongoing MTD decrease that occurs after treatment termination, hypothesized to be the result of the different responses to treatment of proliferative and quiescent cells. Post-treatment decreases in MTD were particularly obvious in patients treated with PCV chemotherapy (8). Second, the PCV dataset was the most complete, with the longest observation period and the most observations per patient before and after treatment.

Model development

The final selected model is shown in Figure 2 and relies on the following structure. The tumor is composed of proliferative \( (P) \) and non-proliferative quiescent tissue \( (Q) \), expressed in millimeters. The transition of proliferative tissue into quiescence is governed by a rate constant denoted \( k_{PQ} \). The treatment directly eliminates proliferative cells by inducing lethal DNA damage while cells progress through the cell cycle. The quiescent cells are also affected by the treatment and become damaged quiescent cells \( (Q_P) \). Damaged quiescent cells, when re-entering the cell cycle, can repair their DNA and become proliferative once again (transition from \( Q_P \) to \( P \) ) or can die due to unrepaired damages (14, 15). This hypothesis is consistent with the mechanism of action of CCNU and procarbazine, which are alkylating agents considered to be cell-cycle non-specific drugs that induce DNA damages in both proliferative and quiescent cells (9).

We modeled the pharmacokinetics of the PCV chemotherapy using a kinetic-pharmacodynamic approach, in which drug concentration is assumed to decay according to an exponential function (16). In this model, we did not consider the three drugs separately. Rather, we assumed the treatment to be represented as a whole by a
unique variable \((C)\), which represents the concentration of a virtual drug encompassing the three chemotherapeutic components of the PCV regimen. We modeled the exact number of treatment cycles administered by setting the value of \(C\) to 1 (arbitrary unit) at the initiation of each cycle \((T_{Treat})\): \(C(t = T_{Treat}) = 1\).

The resulting model is as follows:

\[
\frac{dC}{dt} = -KDE \times C
\]
\[
\frac{dP}{dt} = \lambda_P \times P \left(1 - \frac{P^*}{K}\right) + k_{QPP} \times Q_P - k_{PQ} \times P - \gamma_P \times C \times P
\]
\[
\frac{dQ}{dt} = k_{PQ} \times P - \gamma_Q \times C \times Q
\]
\[
\frac{dQ_P}{dt} = \gamma_Q \times C \times Q - k_{QPP} \times Q_P - \delta_{QP} \times Q_P
\]
\[
P^* = P + Q + Q_P
\]

The parameter \(KDE\) is the rate constant for the decay of the PCV concentration in plasma, denoted \(C\). \(\lambda_P\) is the rate constant of growth used in the logistic expression for the expansion of proliferative tissue (see below). The drug concentration \((C)\) is assumed to induce DNA damages in both proliferative and quiescent tissue through linear functions (damages in proliferative and quiescent tissue are denoted \(\gamma_P\) and \(\gamma_Q\), respectively). We assumed \(\gamma_P = \gamma_Q = \gamma\) for identifiability reasons. However, this hypothesis can be justified by the fact that the basic action of the treatment may not depend on the cell-cycle status (proliferative or quiescent) \((9)\).

We tested different expressions (linear, exponential, logistic, generalized-logistic and Gompertz) for the growth of the proliferative tissue. A logistic term with a fixed maximal tumor size \((K)\) of 100 mm provided the best results in terms of the objective function, and 100 mm is consistent with the maximal MTD usually observed in LGG patients \((7)\).

The parameter \(k_{QPP}\) denotes the rate constant for transfer from damaged quiescent tissue to proliferative tissue, and \(\delta_{QP}\) denotes the rate constant for elimination of the damaged quiescent tissue.
The model parameters were estimated by fitting the model solution $P + Q + Q_p$ to the actual MTD values. The resulting set of parameters to be estimated was

$(\lambda_p, k_{pq}, k_{q,p}, \delta_{q,p}, \gamma, KDE)$ with two additional initial conditions, $P_0 = P(t = 0)$ and $Q_0 = Q(t = 0)$, where time $(t = 0)$ corresponds to the first available data. We assumed $Q_{P_0} = Q_p(t = 0) = 0$ in the absence of treatment.

The individual parameters corresponding to the eight population parameters (six parameters + two initial conditions) were assumed to be log-normally distributed across individuals. For example, for the efficacy parameter $\gamma$, we set $\gamma_i = \gamma \times \exp(\eta_i)$, where $\gamma$ is the mean (population) value, $\gamma_i$ is the individual parameter value, and $\eta_i$ represents the deviation for the individual $i$ from the mean value. $\eta$ are random variables with mean 0 and variance $\Omega$, estimated as part of the population parameters and expressed as coefficient of variation (CV) in percent. The variability on $KDE$ was fixed. All remaining parameters were estimated with their inter-individual variability. We assumed potential correlations between the random effects. Patient characteristics such as sex, tumor type (oligodendroglioma, oligoastrocytoma or astrocytoma), age at diagnosis and age at treatment onset were tested as potential covariates of model parameters.

In this model, $\lambda_p$ (the rate constant of growth for the proliferative tissue) and $k_{pq}$ (the rate constant for transition from proliferation to quiescence) are considered to be tumor-specific parameters, as in the absence of treatment, the model system shrinks to a system in which only these two parameters regulate tumor growth. The remaining parameters $(k_{q,p}, \delta_{q,p}, \gamma, KDE)$ can be considered as treatment-related parameters. Note, however, that all parameters regulate together the characteristics of tumor response to treatment, especially tumor shrinkage and duration of response.

**TMZ chemotherapy and radiotherapy.** Using the model structure developed for the analysis of the PCV data, we analyzed separately the data from patients treated with TMZ chemotherapy and the data from patients treated with radiotherapy. TMZ (like CCNU and procarbazine) is an alkylating agent and thus is considered to be cell-cycle non-specific. Radiotherapy is also known to be cell-cycle non-specific and to induce DNA damages in both proliferative and quiescent cells (9). Therefore, it seemed to us justified to model these two treatments using the model structure developed for PCV.
chemotherapy. For TMZ chemotherapy, however, because the treatment scheduling was much more variable between patients, we did not take into account the number of cycles administered to the patients. We only considered a single treatment cycle and set the virtual TMZ concentration to 1 at the time of treatment initiation. MTD in patients treated with radiotherapy was ultimately modeled in the same way. We did initially attempt to model the effect of radiation differently by relying on an on/off-switching hypothesis. Specifically, we initially assumed that during the treatment period, the tissue was affected through the parameter $\gamma$, and outside the treatment period this effect was removed, i.e., $\gamma$ was set to 0. However, we later adopted the use of the kinetic-pharmacodynamic approach, as it did not affect the objective function and enabled us to compare parameter values across treatments.

Results

Model parameter estimates and model evaluation

The selected structural model (Figure 2) successfully described the tumor size dynamics before, during and after treatment in patients treated with first-line PCV chemotherapy and also in patients treated with first-line TMZ chemotherapy or first-line radiotherapy. Figure 3 shows predicted MTD values plotted against observed MTD values for all patients in each of the three groups and reveals a strong correlation between predictions and observations, showing that the model correctly reproduced, without any apparent bias, the observed MTD values. Figure 4 depicts the observed MTD values together with the model predictions, using the individual parameters of three representative patients from each treatment series. Again, a strong correlation was evident between the observed and the predicted evolution patterns of the MTD in these patients.

We carried out sensitivity analysis for the model in the 21 patients treated with PCV. This analysis consisted of repeating the estimations while leaving out one patient's data in each repetition. It appears that no single patient substantially influenced the estimation (results shown in the supplementary data: “Sensitivity of parameter estimates” and Figure S2).
We also investigated the effect of the choice of the variability level of parameter *KDE*, the rate constant for the decay of the PCV concentration in plasma. We initially attempted to estimate the variability on *KDE*, but its estimation was found to be associated with a high standard error and a worsening of the objective function. For these reasons, we assigned a fixed value to the variability. In the model, we set this variability level at a high percentage, 70%, in order to accommodate the simplistic approach used to model treatment pharmacokinetics. However, further analysis shows that parameter estimates are not significantly affected when this variability is set to 0 (supplementary data: “Sensitivity of parameter estimates” and Figure S3).

We also used the stepwise-backward strategy (17) to investigate whether any patient characteristics functioned as model covariates; none of the examined characteristics was identified as a covariate.

As shown in Table 1, consistent with the model’s assumption that $\lambda_p$ and $k_{pQ}$ are tumor-specific, the independent estimation of these two parameters resulted in consistent values across the three data series. The basic doubling times of the size of the proliferative tissue, expressed as the inverse of the growth parameter ($1/\lambda_p$), were estimated to be 8.3, 8.8, and 7.3 months for the PCV, TMZ and radiotherapy data series, respectively. The growth rate of the proliferative tissue was estimated to be 4 to 5.5 times higher than its quiescence rate.

For patients treated with radiotherapy, we initially estimated that the rate of transition of damaged quiescent tissue into a proliferative state ($k_{Q_PQ}$) was very low ($<10^{-5}$). This seems to indicate that quiescent cells that have sustained DNA damages from radiotherapy are likely to die when re-entering the cell cycle. This estimation, however, was associated with a substantial relative standard error ($>100\%$). For PCV and TMZ chemotherapy, we estimated that 20–25% of damaged quiescent cells could repair their lesions to reconstitute the pool of proliferative cells.

**External validation and potential for prediction**

To investigate the validity of the model, we used the data from the remaining 96 patients treated with TMZ who were not included in the sample for parameter estimation. We
compared the MTD time course observed in this series with the MTD time course simulated with the model using the parameter estimates of the original sample of 24 patients treated with TMZ. The results of this analysis, presented in Figure 5 (left panel), show good agreement between the 5%, 50% and 95% observed percentiles and the 5%, 50% and 95% simulated percentiles of the MTD time course.

We then explored the model’s ability to predict treatment efficacy in LGG patients on the basis of pre-treatment time-course tumor size observations. To this end, we pooled together the PCV and radiotherapy data to constitute a database of 46 patients. Six LGGs treated with PCV chemotherapy were randomly selected out of the database. We used the remaining 40 patients to estimate population parameters by introducing the type of treatment (PCV chemotherapy or radiotherapy) as a covariate on the efficacy parameter $\gamma$ by following the stepwise-backward method (17). Parameter estimates in the pooled data set were similar to those obtained in previous estimations (see supplementary data: “Sensitivity of parameter estimates” and Figure S4). For the six patients whose data we isolated from the group, we predicted the MTD time course by using the population parameter estimates, except for the tumor-specific $\lambda_p$ parameter, which we estimated for each patient according to his or her individual pre-treatment MTD data. At least two pre-treatment data points are required to estimate this growth parameter. The initial conditions $P_0$ and $Q_0$ were assigned using the actual MTD observation at diagnosis (corresponding to $P_0 + Q_0$) and assuming that the proliferative tissue constitutes 10% of the whole tumor size (18). As shown in Figure 5 (right panel), there was good correlation between the predicted and the observed MTD time courses in these six patients ($r^2 = 0.86, p < 0.001$ for the six patients, representing 52 predictions). This suggests that the model might be used to predict treatment efficacy on the basis of population parameter estimates combined with individual estimations of the tumor growth rate parameter. The six individual prediction profiles are presented in the supplementary data (Figure S5).

Discussion
We have developed a TGI model that successfully reproduces tumor size dynamics of LGG patients treated with chemotherapy (PCV or TMZ) or radiotherapy. The slow growth of LGGs and the ongoing response that is frequently observed after treatment
termination led us to formulate a model that was more complex than the existing TGI models for NSCLC and colorectal cancer, which use linear (2) or exponential functions (4) to model tumor growth. Those simple models would be insufficient to reproduce our data, and specifically, they would be unable to capture the prolonged response of the tumor following cessation of treatment. We provide a biological interpretation for this prolonged response, attributing it to delayed treatment action on quiescent cells as compared with proliferative cells, and represent it in our model by incorporating both proliferative (P) and quiescent cell populations. These populations respond differently to the therapeutic modalities typically used in the treatment of LGG, which all function by damaging the DNA of both cells in both populations (9).

The model is composed of four ordinary differential equations and incorporates six parameters and two initial conditions. Two parameters (λ₀ and k₀) are considered to be tumor-specific parameters, as in the absence of treatment the complexity of the model shrinks to a system regulated by these two parameters alone. The remaining four parameters are considered to be treatment-related parameters.

Importantly, independent analyses of patients treated with PCV chemotherapy, TMZ chemotherapy or radiotherapy produced similar estimates of tumor-specific parameters (λ₀ and k₀). Estimated parameters were also consistent with known biological characteristics of LGG: For example, according to the model, LGGs mostly consist of quiescent cells. Estimates indicated that the initial proliferative tissue represented 2% of the tumor in the TMZ series, 9% in the radiotherapy series, and 15% in the PCV chemotherapy series (see Table 1). In LGG, the proliferative tissue, as measured by Ki-67 labeling, is typically <5%; however, Ki-67 labeling indices of up to 10% have been observed (18). Furthermore, the Ki-67 labeling index might under-represent the quantity of proliferative tissue (19), and studies using MCM2 labeling have shown that approximately 9% of the LGG may be proliferative tissue (20). Indeed, MCM2 stains not only cycling cells but also cells that are licensed for DNA replication. Biological validation of the model will require an investigation of the correlation between λ₀ (the growth rate of the proliferative tissue) and quantities of proliferative tissue observed through Ki-67 labeling. It will also be important to assess whether taking into account molecular characteristics of LGG, namely, the 1p/19q codeletion status, the IDH1
mutation status and the MGMT methylation status (21), might improve the model's accuracy.

A particularly interesting aspect of our model lies in its ability to simulate the time course of the quantity of proliferative tissue in treated LGG. As the proliferation index in LGG has been correlated with the ratio of choline/N-acetylaspartate (NAA), measured using magnetic resonance imaging spectroscopy (22), assessment of the choline/NAA ratio time course in treated LGG could be used to validate our model's predictions regarding the growth patterns of proliferative tissue. The validated model could then be used as a simulation tool to conceive potentially more effective treatment schedules. For example, model simulations with different durations of chemotherapy or different time intervals between chemotherapy cycles could assist in identifying chemotherapy schedules with a more prolonged impact on proliferative cells.

Another promising avenue would be to use the model to predict treatment efficacy in LGG patients on the basis of pre-treatment time-course tumor size observations. Simulations of response to different treatments (chemotherapy or radiotherapy for example) or to different chemotherapy regimens (PCV or TMZ for example) could be performed to select the most effective treatment for a given patient. As shown in the present study, preliminary data suggest that such an approach might be feasible, and future studies will have to investigate this potential on a larger number of patients. Finally, we note that previous studies have made significant contributions towards modeling the time and space evolution of gliomas. These models, based on partial differential equations (PDEs), describe the spatio-temporal evolution patterns of tumor cells in the brain as “traveling waves” driven by two processes: uncontrolled proliferation and tissue invasion (23). This proliferation-invasion description has led to the suggestion that tumor diameter grows linearly over time with a velocity given by a combination of the two model parameters (24). Swanson and colleagues showed the relevance of such a model for the prediction of the growth kinetics of untreated gliomas, specifically estimating net rates of proliferation and invasion in vivo for individual patients (25, 26). These parameters were shown to be prognostic of overall survival and predictive of radiotherapy efficacy in glioblastoma (27, 28). Mandonnet and colleagues studied the reliability of this model in determining LGG dynamics (5, 29) and showed it
to be in agreement with the linear evolution of the MTD observed in these tumors before transformation towards a higher grade of malignancy. As mixed-effect modeling techniques cannot be yet applied to PDEs, we were constrained to modeling the dynamic evolution of the MTD using ordinary differential equations, thus omitting any spatial considerations. In the future, the integration of nonlinear time- and space-models of tissue dynamics in a population context will certainly be the most efficient strategy to lead to an integrative, holistic model of LGG response to treatments (30).

In conclusion, we have developed a model of tumor growth inhibition that, to our knowledge, is the first to successfully describe the time course of tumor size in LGG patients treated with chemotherapy or radiotherapy. We believe that this model constitutes an important step towards developing rational strategies for predicting treatment efficacy and optimizing treatment schedules in LGG patients.

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Figure legends

Figure 1: Mean tumor diameter (MTD) observations in patients treated with PCV chemotherapy (top), TMZ chemotherapy (middle) and radiotherapy (RT) (bottom) as a function of time in months. Each column shows the trajectories of multiple patients who had similar MTDs at diagnosis. Time 0 corresponds to the time of treatment onset. In 19 patients treated with PCV (90%), 21 patients treated with radiotherapy (84%), and 21 patients treated with TMZ (87%), treatment was started only after a follow-up period lasting up to several years.

Figure 2: Schematic view of the model. $P$ denotes the proliferative tissue and $Q$ the non-proliferative or quiescent tissue. Proliferative tissue is assumed to transition to quiescence at a rate constant $k_{PQ}$. The treatment concentration, calculated from the individual dose through an exponential decay with the rate constant $KDE$, affects both proliferative and quiescent tissue. The tissue composed of cells in proliferation ($P$) is directly eliminated due to lethal DNA damages induced by the treatment. Non-proliferative tissue ($Q$) is also subject to DNA damages due to the treatment. When re-entering the cell cycle, the DNA-damaged quiescent cells ($Q_P$) can either repair their DNA damages and return to a proliferative state ($P$) or die due to unrepaired damages.

Figure 3: Observations versus individual predictions including lines of identity (left) and normalized prediction distribution errors (NPDE) versus time (right) for PCV chemotherapy (top), TMZ chemotherapy (middle) and radiotherapy (RT) (bottom). As expected, the NPDE distribution is similar to a normal distribution with mean 0 and variance equal to 1. The $\epsilon$-shrinkage was 9% for PCV predictions, 7% for TMZ and 14% for radiotherapy.

Figure 4: MTD observed (circles), individual predictions (solid line), and population predictions based on mean parameter values (dashed line) for 3 individuals in each study (top, PCV; middle: TMZ; bottom, RT) selected on the basis of their typical residual error magnitude (the individual's average absolute weight residual is at the population median). Included is the 90% confidence interval around the individual predictions obtained by simulation using the standard errors of the empirical Bayes estimates.
Figure 5: Left panel: Observed 5%, 50% and 95% percentiles on 96 external patients treated with TMZ (dashed line) with the corresponding simulated percentiles using parameters estimated for the initial set of 24 TMZ-treated patients. The simulated percentiles were calculated based on 200 simulations of the model with 200 virtual individuals. Note that the low number of individual measurements after month 22 precludes comparison beyond that time. Right panel: Predicted versus observed MTD data in 6 LGG patients treated with PCV chemotherapy. Different plotting characters are used to distinguish among the 6 patients. MTD values were predicted using pre-treatment MTD data only ($r^2 = 0.86$, $p < 0.001$ for the 6 patients, representing 52 measurements). Pre-treatment MTD data were used to estimate the tumor-specific $\lambda_P$ parameter in each patient. The other parameters were estimated using the population parameters of 40 LGG patients treated with PCV chemotherapy ($n = 15$) or radiotherapy ($n = 25$).

Table 1: Model parameter estimates for patients in the three studies. Parameters are defined in the text. Inter-individual variability (CV) is expressed as percentages. The errors on the estimates are shown in parentheses and were computed as the ratio between the standard error (SE) and the parameter estimate multiplied by 100. The 95% confidence intervals can then be calculated as follows: value $\pm 1.96 \times$SE. The values for tumor-specific parameters ($\lambda_P$ and $k_{PQ}$) were found to be very similar across treatments. For the patients treated with PCV chemotherapy, the median $\eta$-shrinkage was 6% and the maximum value was 29% for parameter $k_{Q_P}$. For TMZ chemotherapy, the median $\eta$-shrinkage was 14%. Parameters $k_{PQ}$ and $\delta_{Q_P}$ were associated with the highest $\eta$-shrinkage (32% and 25% respectively). For radiotherapy, the median $\eta$-shrinkage was 7%. Parameters $KDE$ and $k_{PQ}$ were associated with the highest $\eta$-shrinkage (36% and 23% respectively).
References


PROLIFERATIVE TISSUE

Undamaged quiescent tissue

Damaged quiescent tissue

Lesions repair?

CONCENTRATION

DOSE

KDE

Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.
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<tr>
<th>Parameters</th>
<th>Unit</th>
<th>PCV</th>
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<th>TMZ</th>
<th>Mean value</th>
<th>CV in %</th>
<th>Radiotherapy</th>
<th>Mean value</th>
<th>CV in %</th>
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A Tumor Growth Inhibition Model For Low-Grade Glioma Treated With Chemotherapy or Radiotherapy

Benjamin Ribba, Gentian Kaloshi, Mathieu Peyre, et al.

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