Administration of temozolomide: Comparison of conventional and metronomic chemotherapy regimens

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\textbf{A B S T R A C T}

\textbf{Purpose.} We compare the Maximum Tolerated Dose (MTD) and Metronomic Chemotherapy (MC) protocols for temozolomide administration. We develop an innovative methodology for characterizing optimal chemotherapy regimens.

\textbf{Methods.} We use a PK/PD model based on Faire et al. (2013) for the pharmacokinetics of temozolomide, as well as the pharmacodynamics of its efficacy. For toxicity, which is measured by the nadir of the normalized absolute neutrophil count, we formalize the myelosuppression effect of temozolomide with the physiological model of Panetta et al. (2003b). We introduce a multi-criteria tool for comparing protocols along their efficacy and toxicity dimensions.

\textbf{Results.} We show that the toxicity of the MC regimen proposed by Faire et al. (2013) can greatly be reduced without affecting its efficacy, while the standard MTD protocol efficacy cannot be improved without impairing its toxicity. We also show that for any acceptable toxicity level, the optimal protocol remains closely related to standard MTD.

\textbf{Conclusions.} Overall, our new method enables a rich comparison between protocols along multiple dimensions. We can rank protocols for temozolomide administration. It is a first step toward building optimal individual protocols.

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1. Introduction

The standard approach with chemotherapeutic involves using doses close to the Maximum Tolerated Dose (MTD) in order to maximize the killing of cancer cells. This practice is based on the idea that the chemotherapy efficacy is maximal when drug doses are maximal. MTD doses are administered every 2–4 weeks with a rest period enabling non-cancerous tissues to recover and thereby limiting the toxic effects of drugs. However, these quite long-recovery periods have two main drawbacks. First, even though healthy cells can recover, this is also the case of tumorous tissues. The rest period can therefore foster tumor growth and promote the emergence of resisting cells. Second, angiogenesis contributes to the growth of the tumor, as well as the spreading of metastases and MTD is a drug strategy with weak anti-angiogenic benefits.

The last two decades have seen the development of alternative chemotherapy administration, including the metronomic chemotherapy (MC), (Faire et al., 2013; Kong et al., 2010; Omuro et al., 2013; Wong et al., 2016; Zhou et al., 2007). MC involves low doses, which are comparatively much smaller than MTD and which are administrated on a frequent schedule, without taking a prolonged break. Furthermore, there is empirical evidence that several mechanisms are at stake with MC: (i) the direct effect on tumor; (ii) the inhibition of endothelial proliferation favoring tumor angiogenesis; (iii) a possible stimulation of the immune response. However, there is no clear consensus in clinical trials regarding the actual impact of metronomic strategies. The reason for these ambiguous and sometimes inconsistent effects is related to the multiplicity of the dose levels, schedules and rest periods. There are multiple combinations to be tested and standard empirical trials are of little use for investigating the numerous possibilities. For instance, in the case of CAIRO3 trial, which is one of the only phase III trials involving metronomic regimens, the impact of the combination of bevacizumab and capcitabine was assessed for patients with colorectal cancer (Simkens et al., 2015). Its results were encouraging, even though they did not help disentangle the metro-
nomic dosing of capcitabine and the antiangiogenic effect of bevacizumab (Kerbel and Grothey, 2015). In this context, there is a growing consensus that mathematical modeling provides a useful ground for performing in-silico tests and finding the best administration regimen (Barbolosi et al., 2016; Benzekry et al., 2015; Bocci and Kerbel, 2016).

In this paper, we investigate the case of temozolomide (Temodal®). Faire et al. (2013) use a PK/PD mathematical model to show that an optimized MC administration strategy may be more efficient than MTD in reducing the tumor size. We look here for the optimal administration strategy, while not only taking into account efficacy but also toxicity. As is standard, efficacy is measured by the tumor size at the end of the protocol and toxicity by the minimal normalized absolute neutrophil count (ANC) over the protocol cycle.1 Designing the optimal protocol therefore involves an objective with multiple criteria, including toxicity and efficacy. Indeed, the optimal protocol should maximize the overall survival, and the event-free survival (Lamborn et al., 2008; Trippa et al., 2015). These survivals have been shown to be negatively correlated with the severity of toxicity (see Bahig et al., 2015 for the prostate cancer for instance) and the tumor size (see Wood et al., 1988). In consequence, our objective should seek for protocols combining a high efficacy – through a low tumor size – and a mild toxicity.

A first solution to handle such multidimensional objectives is to combine them into a unique well-defined objective using an aggregation function. The aggregation function maps for any protocol, its associated efficacy and toxicity into a real quantity that is easily comparable to other similar quantities. The issue with this approach is that it involves arbitrariness in the choice of the aggregation function. How should we determine its functional shape, the functional parameters? Our first contribution in this paper is to propose a methodological approach to handle optimization with multi-criteria objectives without using aggregation. To do so, we introduce the concept of Pareto-efficient protocols, which correspond to the protocols maximizing efficacy for given levels of toxicity. In other words, given a Pareto-efficient protocol, there is no other protocol improving simultaneously both dimensions: yielding a better efficacy and a less severe toxicity.

Introducing the concept Pareto-efficient protocols delivers two main insights. First, instead of obtaining a unique optimal protocol whose interpretation may rely on some arbitrary choices, our optimization provides a set of Pareto-efficient protocols, where each of them offers a best possible compromise between toxicity and efficacy. Second, this set of Pareto-efficient protocols offers also the possibility to assess the benefit in terms of tumor reduction of a more severe toxicity, or equivalently the loss in efficacy of a decrease in toxicity severity. It helps assess whether an increase in toxicity severity is likely to be worthwhile or to anticipate on the efficacy loss following a reduction in toxicity severity.

Determining the Pareto-efficient strategies enables us to classify any protocol and determine whether it can be improved – in other words, if a protocol with a similar toxicity severity exists, while offering a better efficacy. In particular, this allows us to participate in the debate between MC and MTD protocols. We show that the MTD protocol (200 mg/m²/day D1–D5 on 28 days) analyzed in Faire et al. (2013) is Pareto-efficient among all strategies that we investigated. We could not find how to improve efficacy without impairing toxicity. Conversely, the MC protocol proposed in Faire et al. (2013) is not Pareto-efficient. Indeed, some protocols offer a less severe toxicity than MC, while achieving a similar efficacy. After 56 weeks, the MC protocol achieves a prohibitively severe toxicity, while our Pareto-efficient protocol achieves a milder and tolerable toxicity. Our results contrast with Faire et al. (2013), who do not take toxicity into account.2 Our methodological contribution may prove to be a helpful device in the debate between MC and MTD protocols and more generally in highlighting the trade-offs related to the selection of protocols – not only for temozolomide but other drugs.

2. Materials and methods

2.1. PK/PD model

We use the model of Faire et al. (2013) for the pharmacokinetics of temozolomide, as well as the pharmacodynamics of efficacy. Pharmacokinetics is modeled as a standard one-compartment model with a first-order absorption, as was originally proposed in Panetta et al. (2003a). The pharmacodynamics relies on an interface model, pioneered by Meille et al. (2008). The model embeds two interfaces, for endothelial and cancer cells, since temozolomide affects both types of cells differently. Cells are only affected when the plasma drug concentration is above a given threshold and the threshold for endothelial cells is smaller than the one for cancer cells reflecting that the former are more sensitive to temozolomide than the latter. The efficacy, modeled by the tumor mass, is assumed to follow a Gompertz model in absence of treatment – the calibration is such that the tumor mass doubles within 40 days in absence of treatment. The modeling of the treatment impact on tumor growth reflects both cytotoxic and anti-angiogenic effects. These cytotoxic effects are dampened down by drug resistance of cancer cells.

The main toxicity effect of temozolomide is myelosuppression, which implies a stoppage of bone marrow activity. Connecting the toxicity measure related to absolute neutrophil count (ANC) to area under the curve of temozolomide plasma concentration (AUC) was partly successful (Hammond et al., 1999), but was unfortunately found to only provide a partial picture of the total effect (Panetta et al., 2003b). For properly modeling ANC and temozolomide myelosuppressive effects, Panetta et al. (2003b) have proposed a physiological model of haemopoiesis, based on those of Minami et al. (1998) and Friberg et al. (2000). Haemopoiesis is modeled as a three-compartment model reflecting the successive development stages of proliferating cells in the bone marrow, from pluripotential stem cells to differentiated blood cells (platelets, red blood cells, and white blood cells). The growth of proliferating cells is affected by the feedback effects of the granulocyte colony stimulating factor (G-CSF): a low ANC implies a large growth rate and vice versa. Finally, the toxicity effect of temozolomide is binary. Either temozolomide has no effect as long as its plasma concentration remains below a given threshold, or temozolomide completely shuts down the growth of proliferating cells in the bone marrow, which in turns harms the number of ANC through the maturation process. We provide an exhaustive mathematical formulation of the model, as well as the parameter calibration, in Appendix, Section 1.

2.2. Simulations

We simulate the PK/PD model over a time window of 392 days. This time horizon covers slightly more than one year and is a multiple of standard protocol cycles (28 or 56 days), which avoids ar-

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1 In appendix, we use a two-dimensional measure of toxicity including not only the minimal normalized ANC but also the area under the curve of the plas-
matic concentration (AUC). The correlation between AUC and ANC is informa-
tive about the drug toxicity (Panetta et al., 2003b), even though this is imperfect (Hammond et al., 1999).

2 These results rely on the calibration, in particular for the pharmacodynamics of the toxicity. We discuss these aspects in greater detail in Section 3.3.
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