Administration of temozolomide: comparison of conventional and metronomic chemotherapy regimens

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Abstract

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.

Methods. We use a PK/PD model based on Faivre and coauthors [9] 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 and coauthors [25]. We introduce a multi-criteria tool for comparing protocols along their efficacy and toxicity dimensions.

Results. We show that the toxicity of the MC regimen proposed by Faivre and coauthors [9] 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.

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.

Keywords: Pharmacokinetics, Pharmacodynamics, Modelization, Multi-criteria decision-making, Metronomic chemotherapy.

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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 to 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), [9, 15, 22, 30, 32]. 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 capecitabine was assessed for patients with colorectal cancer [27]. Its results were encouraging, even though they did not help disentangle the metronomic dosing of capecitabine and the antiangiogenic effect of bevacizumab [13]. 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 [2, 4, 5].

In this paper, we investigate the case of temozolomide (Temodal®). Faivre and coauthors in [9] use a PK/PD mathematical model to show that an opti-

mized 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 [18, 29]. These survivals have been shown to be negatively correlated with the severity of toxicity (see [1] for the prostate cancer for instance) and the tumor size (see [31]). 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

[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 plasmatic concentration (AUC). The correlation between AUC and ANC is informative about the drug toxicity [25], even though this is imperfect [12].

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/m^2/day D1-D5 on 28 days) analyzed in [9] 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 [9] 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 [9], 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 Faivre and coworkers [9] for the pharmacokinetics of temozolomide, as well as the pharmacodynamics of efficacy. Pharmacokinetics is modelled as a standard one-compartment model with a first-order absorption, as was originally proposed in Panetta et al. [24]. The pharmacodynamics relies on an interface model, pioneered by Meille and coworkers [20]. 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, modelled by the

[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.

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 modelling 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 plasmatic concentration (AUC) was partly successful [12], but was unfortunately found to only provide a partial picture of the total effect [25]. For properly modelling ANC and temozolomide myelosuppressive effects, Panetta and coworkers [25] have proposed a physiological model of haemopoiesis, based on those of Minami et al. [21] and Friberg et al. [11]. Haemopoiesis is modelled 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 plasmatic 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 artifacts in results related to end-of-period effects.[3] All computations are implemented in C++. Each protocol is evaluated through its efficacy and toxicity that are computed as follows.

[3]Typically, a protocol whose treatment ends at day 392 will be favored compared to a protocol whose rest period ends at day 392. By setting a period of 392 days and focusing only on protocols whose cycle length divides 392, we avoid such phenomena.

- *Efficacy:* the tumor size (in grams) at day 392. The smaller the tumor size, the higher the efficacy.

- *Toxicity:* the nadir, *i.e.*, minimal, normalized ANC (in %) obtained between day 0 and day 392. A small nadir implies a severe toxicity.

2.3 Protocols

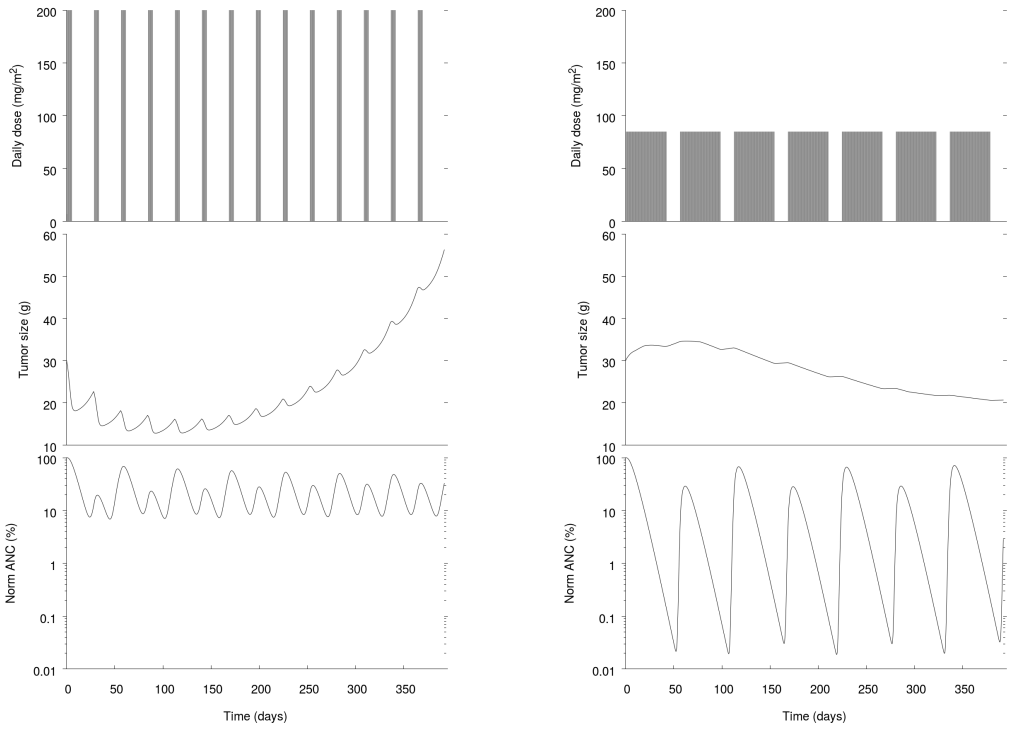
All protocols that we consider consist of two phases. First, a treatment phase implies the administration of a dose d, expressed in mg/m^2/day, from day 1 to day D. Second, the treatment is followed by a recovery period from day $D+1$ to day D_{tot}, where D_{tot} is the total cycle length. We will denote such a protocol as $\{D_{tot}, (d, D)\}$.

The MTD protocol studied in [9] consists in the administration of a dose of 200 mg/m^2/day from day 1 to day 5, for a cycle of 28 days. With our notation, the MTD protocol will be denoted $\{28, (200, 5)\}$. Similarly, the MC protocol also studied in [9] will be denoted $\{56, (85, 42)\}$. Indeed, it corresponds to 85 mg/m^2/day from day 1 to day 42, for a total cycle of 56 days.

In Figure 1, we display the output for the MTD $\{28, (200, 5)\}$ (Figure 1a) and MC $\{56, (85, 42)\}$ (Figure 1b) protocols, over our observation period of 392 days, corresponding to 7 MC or 14 MTD cycles. In Figures 1a and 1b, the top graph represents the daily dose, the middle graph the tumor size – and thus the protocol efficacy – while the bottom graph represents the normalized ANC.

We can see from Figure 1 that the efficacy of both protocols are similar to those in [9].[4] After 392 days, the efficacy of the MC protocol (tumor size: 20.7 grams) is better than the one of MTD (tumor size: 56.3 grams). However Figure 1 brings new insights regarding toxicity. The greater efficacy of MC, compared to MTD, comes at the cost of a much more severe toxicity: the normalized ANC nadir is 0.02% for MC compared to 6.87% for MTD. Indeed, [17] defines that an ANC of 1500 cells/mm^3 should be considered to be abnormally low and severe infections occur at values below 500 cells/mm^3. This threshold of 500 cells/mm^3 typically leads the treatment to be interrupted. Since a typical ANC value is approximately 7,000-8,000 cells/mm^3 [8], a normalized ANC nadir around 6 to 7% can be considered as a lower bound.

[4] We use the same calibration, pharmacokinetics and pharmacodynamics for efficacy.



(a) MTD protocol $\{28, (200, 5)\}$ (b) MC protocol $\{56, (85, 42)\}$

Figure 1: Output for two protocols. Top: Protocol daily dose (mg/m^2). Middle: Tumor size (g). Bottom: normalized ANC (% of date-0 ANC).

At this stage, a comment about toxicity is necessary. As explained above, temozolomide has an impact on toxicity through a stoppage of the growth of proliferating cells in the bone marrow. This stoppage occurs whenever the plasmatic concentration of temozolomide is above a given threshold. But once this toxicity threshold has been crossed, temozolomide has no further toxic effect. The toxicity threshold being calibrated to a low value, the growth stoppage is rapidly triggered for both MTD and MC protocols. Also, since temozolomide has a short half-life in the plasma (less than two hours, [23, 24]), the toxic effects stop short after the treatment stopped for both MTD and MC protocols. In consequence, the ANC value is then mainly driven by the treatment length. Since the treatment length of the MC protocol is much longer than of the MTD one, normalized ANC reaches much lower values for the former than the latter, which explains the toxicity results. In consequence, the toxicity threshold value is crucial for quantifying toxicity effects. Our calibration stems from the work of Panetta and coworkers [25]. Their medical

trial, on which they base their calibration, involves a MTD-like protocol and no MC-like protocol. This may explain why the value of the toxicity threshold is so low, which may come at the expense of MC-like protocols. Clinical trials involving MC-like protocols for temozolomide (see [6, 14, 22, 26] for adults and [3, 28] for children) seem to conclude that MC-like protocols are tolerated, even though they exhibit heterogeneous efficacy (from improvement over MTD to no efficacy). Further studies about the toxicity parameters – and their variability – would be necessary to confirm or infirm our results even though our methodology would remain valid. As a robustness check for the estimation, we report in Tables S.2, S.3, and S.4 in Section 3 of the Appendix, the sensitivity of efficacy and toxicity measures for MC and MTD to a $\pm 1\%$ variation in parameter values.

2.4 Ranking protocols: A Pareto approach

Comparing any two protocols involves comparing two combinations of toxicity and efficacy. Unfortunately, there is no unambiguous ranking for such objects. Indeed, consider for instance two protocols P_1 and P_2 with P_1 having a greater efficacy than protocol P_2, but also a greater toxicity. With no further information, whether protocol P_1 should be preferred to protocol P_2 is a matter of appreciation.

A first solution to overcome this difficulty would be to aggregate toxicity and efficacy of any protocol into a unique score value, using a given score function. This score function would map any pair (efficacy, toxicity) to a real number, such that higher scores would correspond to preferred protocols. Reflecting the overall objective, the score should be increasing in efficacy and decreasing in toxicity severity. A straightforward example of such a score function is the weighted sum "efficacy $- \alpha \times$ toxicity", where the weighting parameter $\alpha \geq 0$ characterizes the relative importance of toxicity severity with respect to efficacy. Obviously, the value of α has a strong influence on the final score and the ranking. For small values of α, the score will favor protocols with a high efficacy, while for high values, it will favor protocols with a mild toxicity. However, setting α is subject to some arbitrariness and more generally, so is setting the functional shape of the score function. These choices will dramatically influence, in a non-transparent way, the final selection of optimal protocols.

In order to avoid such arbitrariness, we decided to use a belief-free criterion: Pareto-domination. A protocol P_1 will be said to Pareto-dominate another protocol P_2 if the efficacy of P_1 is greater than (or equal to) the one of P_2 and the toxicity of P_1 is milder than (or equal to) the one of P_2.[5] The advantage of such an approach is that it does not require any prior on the relative weight of efficacy and toxicity. However, the drawback is that not any two protocols can be compared to each other. For instance, if the efficacy of protocol P_1 is better than the one of protocol P_2 but if the toxicity of P_1 is more severe than the toxicity of P_2, then neither P_1 will Pareto-dominate P_2, nor P_2 will Pareto-dominate P_1. The consequence of this limitation is that the optimization will generally not result in a unique optimal protocol but in a set of optimal protocols with different combinations of toxicity and efficacy, which make these protocols not comparable to each other. A protocol will be optimal in the sense of Pareto-domination if there does not exist a protocol offering a better efficacy without impairing toxicity or equivalently a less severe toxicity without degrading efficacy. Such a protocol will be said to be Pareto-efficient. The set of Pareto-efficient protocols is the Pareto frontier.

The Pareto frontier offers several advantages. First, as already said, it is belief-free and outcomes are not affected by a prior choice. Rather than a unique protocol, our optimization yields a set of protocols, offering different compromises between toxicity and efficacy. Second, each of the optimal protocols is Pareto-efficient. Hence, a practitioner can decide upon an maximal admissible level of toxicity and the Pareto frontier will determine the protocol with the best efficacy for the chosen toxicity severity. Alternatively, she can target a tumor size and the Pareto frontier will provide the least toxic protocol achieving the desired efficacy. Third, the Pareto frontier enables to quantify the efficacy variations implied by a planned change in toxicity. Therefore, it allows to assess the value of efficacy in terms of toxicity.

The concept of Pareto-efficiency has initially been introduced in economics

[5]We present here the Pareto approach with two dimensions (one for efficacy and one for toxicity), but it could easily be extended to any finite number of dimensions. For instance, we present in Appendix, Section 5, the case of toxicity measured by two variables. Then, a protocol P_1 will be said to Pareto-dominate another protocol P_2 if the efficacy of P_1 is better than (or equal to) the one of P_2 and every dimension of the toxicity severity of P_1 is lower than (or equal to) the corresponding toxicity measure of P_2. Plotting protocols will involve three dimensions – one for efficacy and two for toxicity – and will therefore imply 3-dimensional graphs. However, our whole reasoning could straightforwardly be extended at almost no cost.

to characterize allocations of resources among a group of participants. A Pareto-efficient allocation is such that it cannot be modified without impairing at least one participant. Consider for instance the allocation of 100 units of resources between two individuals. The allocation $(50, 50)$ (50 units to each individual) is Pareto-efficient since it cannot be modified without depriving an individual of some resources. Contrarily, the allocation $(50, 40)$ is not Pareto efficient, since 10 units of resources have not be allocated. We can increase the allocation of one individual without impairing the other one. Of note, the notion of Pareto-efficiency is silent about equity. Allocation $(100, 0)$ and $(0, 100)$ are also Pareto-efficient. More generally, any Pareto-efficient allocation is of the form $(x, 100 - x)$ where $x \in [0, 100]$. The Pareto frontier is the collection of Pareto-efficient allocations, which is $\{(x, 100 - x) : x \in [0, 100]\}$ in our example. See [19] (chap. 10) and [16] (chap. 8 and 15) for standard references. We have adapted the concept of Pareto-efficiency to protocols. In both cases, it achieves the ranking of multi-dimensional objects: allocations among a group of individuals in one case and multi-dimensional outputs of protocols in the other case.

3 Results

Before presenting the results of our simulations, we start with describing the different protocol families we investigate.

3.1 Protocol families

The protocols that we investigate are either protocols with a finite cycle of 28 or 56 days or protocols without any cycle (or equivalently, with a non-finite cycle length).[6] These protocols can adopt any dose and any treatment length. We will denote protocols with a cycle of 28 (resp. 56) days as *Cycle28* (resp. *Cycle56*), while protocols without cycle will be called *NoCycle*. Formally, these protocols can be parametrized as follows.

[6] In addition to the three families of protocols described above, we also looked at protocols with a cycle of 49 days – since 49 divides 392, our observation length –, but they did not deliver any interesting results. Furthermore, we also applied genetic and swarm particle optimization techniques to obtain Pareto-efficient protocols. All the protocols we could find were very close to the MTD protocol, sometimes slightly dominating but taking advantage of end-of-period effect.

- *Cycle56* corresponds to protocols denoted $\{56, (x, y)\}$, with x mg/m^2/day from day 1 to day y with a cycle length of 56 days. The dose x is any quantity between 0 and 200 mg/m^2/day and y can be any number of days between 1 and 56 days. Note that for $x = 85$ mg/m^2/day and $y = 42$ days, Cycle56 is the MC protocol.

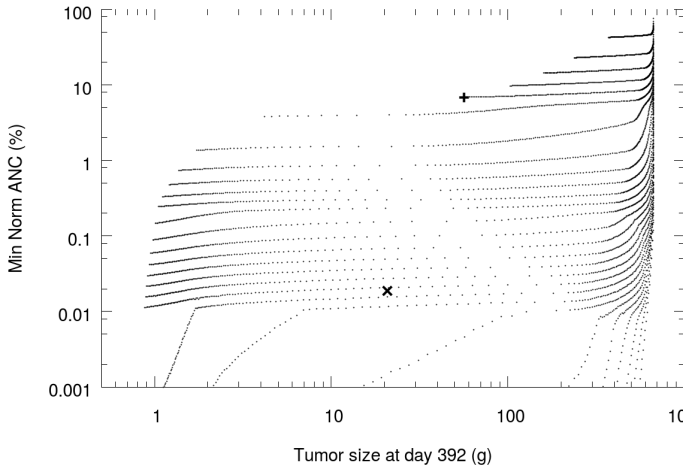
- *Cycle28* similarly corresponds to protocols $\{28, (x, y)\}$. Quantities x and y have the same interpretation as with Cycle56, eept that y has to be smaller than 28 days, the cycle length. We obtain the MTD protocol for $x = 200$ mg/m^2/day and $y = 5$ days.

- *NoCycle* characterizes the protocols $\{\infty, (x, y)\}$, with an absence of cycle – which formally corresponds to an infinite cycle length. Again, x and y have the same interpretation, except that y cannot be greater than 392 days, which corresponds to the length of our observation period.

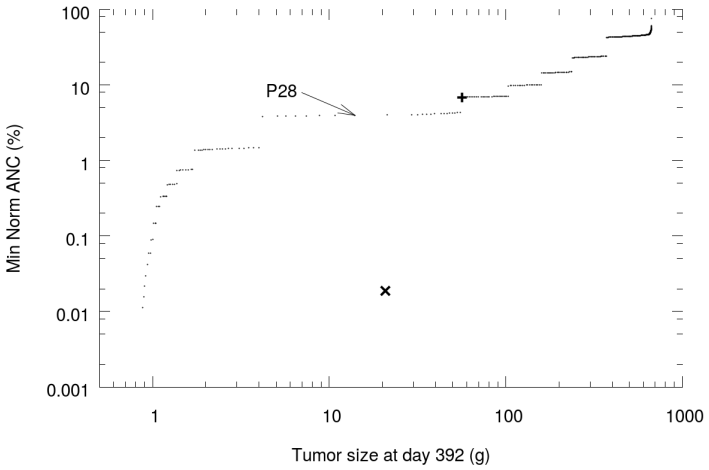
3.2 Simulation results

For each of the three families of protocols (Cycle28, Cycle56, and noCycle), we compute the efficacy and toxicity measures for a large set of protocols. For instance, for protocols of the Cycle28 family of the form $28, (x, y)$, we simulate all protocols for which the dose x varies from 1 to 200 mg/m^2/day (with a step of 1 mg/m^2/day) and the number of treatment days y varies between 1 and 28. In that case, we therefore simulate $28 \times 200 = 5600$ different protocols. We proceed analogously for Cycle56 and NoCycle protocols. In the case of NoCycle protocols, the number of treatment days varies between 1 and 392 (our simulation horizon). Once all feasible protocols have been simulated, we use them to deduce the Pareto frontier, by only keeping protocols for which there is no protocol with a better efficacy and a milder toxicity.

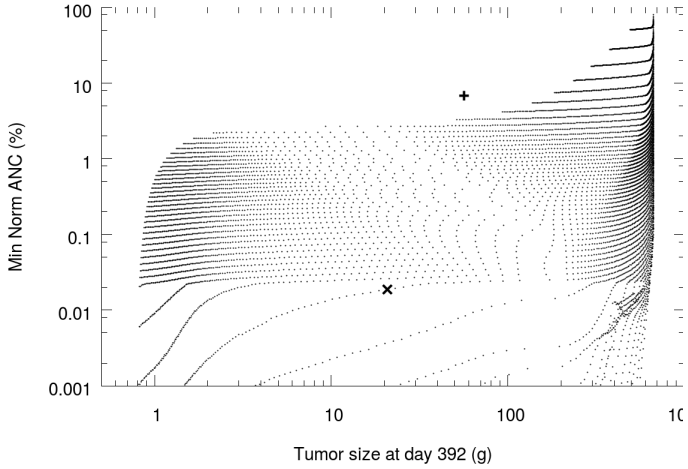
We display the results in Figure 2. Each row corresponds to a different protocol family. The left hand-side panel plots the set of all protocols for the family under consideration. Every dot corresponds to a protocol represented as a pair (efficacy, toxicity). The right hand-side panel plot the Pareto frontier for the given protocol family. Comparing left and right panels makes it visible how the frontier is constructed. Note that for all graphs, we use log-scale for both axis. The plus $+$ and multiplication $\times$ signs correspond to MTD and MC protocols, respectively.



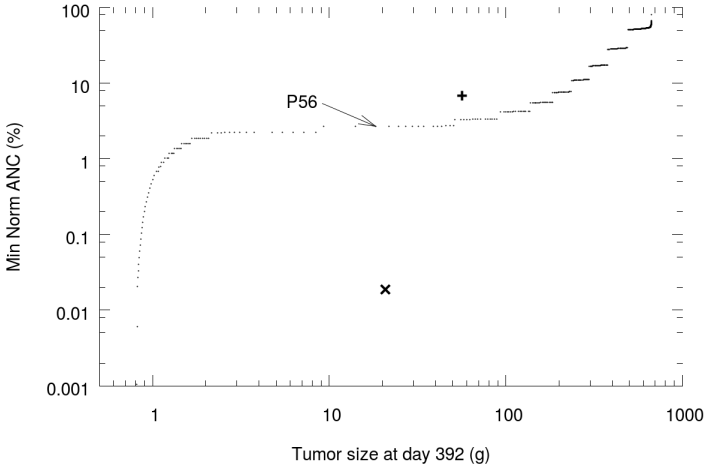
(a) Cycle28 protocols



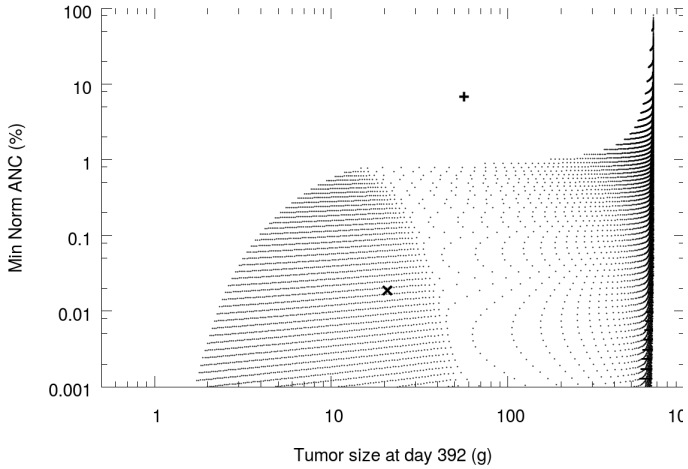
(b) Cycle28 Pareto frontier



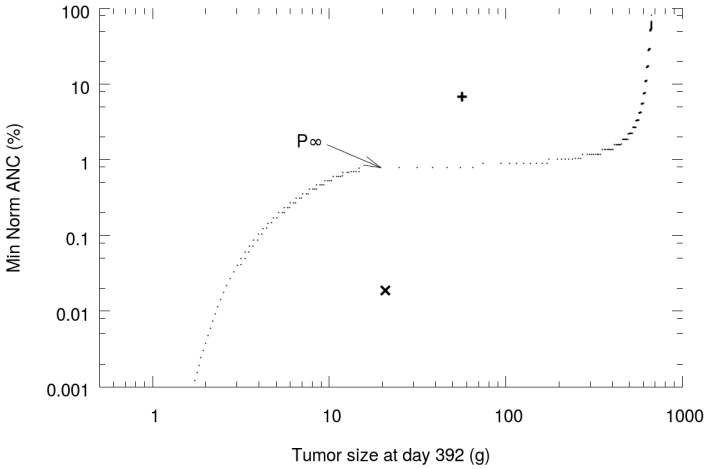
(c) Cycle56 protocols



(d) Cycle56 Pareto frontier



(e) NoCycle protocols



(f) NoCycle Pareto frontier

Figure 2: Representation of (efficacy, toxicity) pairs for the 3 protocol families. +: MTD protocol $\{28, (200, 5)\}$. ×: MC protocol $\{56, (85, 42)\}$.

Figure 2 is an informative representation of Pareto-ordering. Indeed, notice that for a given toxicity severity – or graphically a given y-value –, the further left the protocol, the smaller the tumor mass and the better the efficacy. Conversely, for a given level of efficacy, *i.e.* a given x-value, the further top the protocol, the higher the normalized ANC and the less severe the toxicity. In other words, considering a given protocol P, any protocol located simultaneously above and at the left of P is Pareto-dominating P. This explains the shape of the Pareto frontiers of Figure 2 and how they have been constructed using the scatter plot. We can draw a first lesson from Figure 2. The NoCycle family cannot achieve a as worthy combination of efficacy and toxicity as Cycle28 and Cycle56 families. Formally, it can be checked easily that for any pair of (efficacy, toxicity) achieved by a NoCycle protocol, we can find a Cycle28 or a Cycle56 protocol with a better efficacy and a milder toxicity. Furthermore, we can see that there is no clear ranking between Cycle28 and Cycle56. Indeed, for very severe and very mild toxicity (normalized ANC nadir below 4% or above 50%), Cycle56 protocols achieve the best efficacy, while the opposite holds for medium toxicity severities (normalized ANC nadir between 4 and 50%).

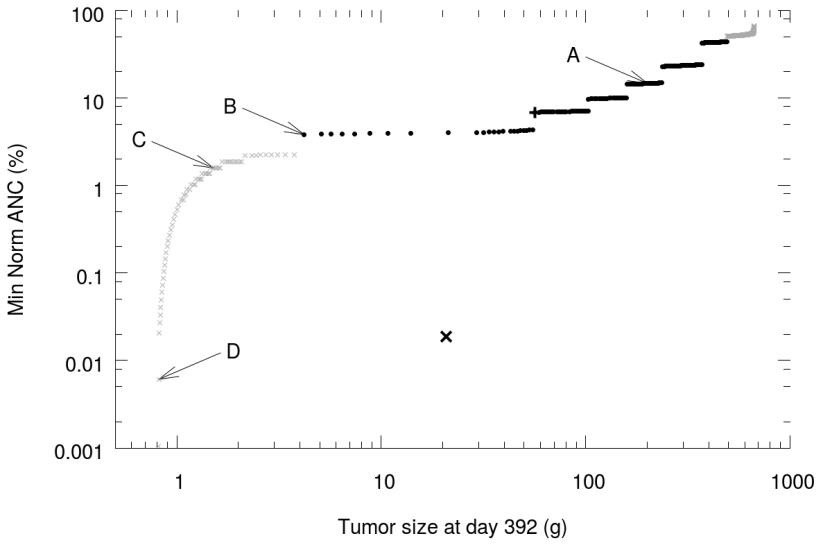


Figure 3: Pareto frontiers for the three protocol families. Grey cross points are Cycle56 while black circle points are Cycle28.

In order to go further, we plot in Figure 3 the Pareto frontier for the three protocol families. By analogy with left and right hand-side panels of Figure

2, this Pareto frontier would correspond to a scatter plot gathering all points of panels 2a, 2c, and 2e. This graph can also be seen as the Pareto frontier of Pareto frontiers from panels 2b, 2d, and 2f. In fact, no globally Pareto-efficient protocol is a NoCycle protocol since they are all Pareto-dominated. When the Pareto-efficient protocol is a Cycle28, it is represented by a black point and when it is a Cycle56, it is represented by a grey cross.

As explained above, the Pareto frontier is also informative about the trade-off between toxicity and efficacy. More precisely, the slope of the Pareto frontier at a given point characterizes the efficacy variation implied by a given toxicity change, for small variations around the initial protocol. Unsurprisingly, Figure 3 shows that efficacy and toxicity always move in the same direction along the Pareto frontier. Switching from a given protocol to another protocol offering a less severe toxicity always implies a decrease in efficacy and *vice-versa*. Furthermore, the relationship between efficacy and toxicity variations is not uniform and strongly depends on the initial protocol. For instance, consider protocol A (on Figure 3) associated to a (large) tumor size at day 392 of 200 grams and a normalized ANC nadir of 12%. Switching to protocol B associated to a tumor size at day 392 of 4 grams implies a more severe toxicity with a normalized ANC nadir of 5%. Switching from protocol A to B enables to divide the tumor size at day 392 by a factor of 50, while the normalized ANC nadir diminishes from 12% to 5% (divided by 2). However, decreasing the tumor size at very low levels can be prohibitive in terms of toxicity. For instance, switching from protocol C to D decreases the tumor size from 1.5 grams to 0.8 gram (divided by 2) but implies an ANC nadir nadir decrease from 1.5% to 0.006% (divided by 200).

In Figure S.1 in the Appendix, we report additional graphs showing how the daily dose, the number of treatment days per cycle, and the total drug dose per cycle evolve along the Pareto-frontier. Results are rather intuitive. First, the daily dose remains almost for all protocols (but the ones yielding to very high tumor sizes) in the range of 150 to 200 mg/m^2/day. Second, the number of treatment days monotonically increases from 1 day (for protocols with the lowest efficacy) to 40 (for protocols with the best efficacy – but obviously the most severe toxicity). Most protocols have a number of treatment days varying between 3 and 10. Finally, the total dose per cycle is also monotonic with the efficacy: protocols with a higher efficacy are associated to a higher total dose.

3.3 MC and MTD protocols

We now discuss more specifically the MC and MTD protocols. We report in Table 1 the associated measures of efficacy and toxicity. We observe that the gains in efficacy observed by [9] for MC compared to MTD have come at the cost of a higher toxicity, which is far too high for the protocol to be acceptable.

	Efficacy	Toxicity
MTD	56.25	6.87
MC	20.69	0.02

Table 1: Efficacy and toxicity measures for MC and MTD protocols

We recall that MTD and MC protocols are reported on Figure 2 with a plus $+$ and a multiplication $\times$ sign. First, Figure 2 makes it clear that for any family, we can find a protocol that performs better than MC, by offering a lower toxicity – which could make the protocol tolerable – for a similar level of efficacy. MC is therefore a Pareto-dominated protocol. Second, regarding MTD, the result is very different. For Cycle56 and NoCycle families, the MTD protocol offers a combination of toxicity and efficacy that cannot be reached by any protocol of the family, as it is clear on panels 2c to 2f. Indeed, any Cycle56 or NoCycle protocol deteriorates either the toxicity or the efficacy compared to MTD. Furthermore, as can be seen on panel 2a, MTD belongs to the Pareto frontier of Cycle28 protocols. Its efficacy cannot be increased without increasing the toxicity severity.

	Family	Protocol	Toxicity (%)	Efficacy (g)
P28	Cycle28	$\{28, (192, 6)\}$	3.96	13.98
P56	Cycle56	$\{56, (197, 9)\}$	2.69	18.28
P∞	NoCycle	$\{\infty, (198, 17)\}$	0.79	19.49

Table 2: Protocols Pareto-dominating MC with a minimal toxicity.

In order to investigate to which extent the MC protocol is Pareto-dominated, we determine for each family, the protocol with the less severe toxicity and an efficacy at least as good as MC (*i.e.* a tumor size at day 392 less than 20.69 grams).[7] Protocols are described in Table 2.

[7]For the sake of completeness, we also display in Appendix, Section 4, the protocol with

Consistently with the Pareto frontier of Figure 3, the protocol of Cycle28 offers the less severe toxicity. In that case, the efficacy is comparable, but the Cycle28 Pareto-efficient protocol implies a potentially admissible – though severe – toxicity. Interestingly, the protocol of interest, $\{28, (192, 6)\}$, is very close to MTD $\{28, (200, 5)\}$. Note that the protocols of the two other families, Cycle56 and NoCycle, are also close cousins of the MTD protocol. As MTD, those protocols feature indeed a daily dose close the maximal tolerated dose of 200 mg/m^2/day and relatively short treatment length.

4 Discussion

In this paper, we propose a new methodological approach to rank protocols along two or several dimensions. We have introduced the concept of Pareto frontier, which characterizes protocols with different though optimal compromises between efficacy and toxicity. The Pareto frontier could guide practitioners by helping them opt for protocols that exhibit the best trade-off between toxicity and efficacy. The practitioner could for instance select a maximal toxicity severity that she considers to be acceptable, and the Pareto frontier will thereby determine the protocol fulfilling the toxicity constraint whose efficacy is maximal.

Besides enabling to rank protocols in terms of efficacy and toxicity, our solution could be extended to account for inter-patient variability in drug absorption. For instance, in the case of temozolomide, the inter-patient variability is known to be significant [24]. Instead of computing Pareto-efficient protocols for an average PK/PD model calibration as we did in this paper, we could take into account patient's reaction to treatment and rely on a personalized calibration of the PK/PD model. This would enable to determine individual Pareto-efficient protocols, and then help move toward personalized oncology. Another route for future extension would consist to apply our methodology to other chemotherapy drugs, such as vinorelbine for instance, for which a clinical study has been developed based on the results of a PK/PD mathematical model [7]. The methodology could similarly be applied to drug combinations,

the best efficacy and a toxicity not more severe than MC (*i.e.* nadir of normalized ANC higher than 0.02%). The three protocols are respectively denoted P28, P56 and P∞. They are reported on Figure 2. The time-series evolution for tumor size and ANC of these three protocols can be found in Figure S.4 of Appendix, Section 5.3.

such as cisplatin plus etoposide, used for treating small-cell lung cancer, for which a mathematical model has been developed [10].

To conclude, let us come back to one of results. In the debate between MC and MTD for temozolomide, we show that, given the literature model calibration, MC is Pareto-dominated and protocols with a similar efficacy but a much lower toxicity can be found. However, it should not be deduced from our results that MC protocols are always meant to be Pareto-dominated. Our contribution is mainly methodological and it is noteworthy to recall the possible shortcomings of the literature calibration we have opted for. Parameters have not been all tested extensively. Furthermore, the estimation of parameters for the PD model of toxicity relies on a clinical trial involving only protocols that are close to MTD, which lead to an overestimation of toxicity for MC-like protocols. A final difficulty with the parameter estimation is the significant inter-individual and inter-occasion variability reported in clinical trials [24]. Since the estimation we rely on does not embed any variability, this may yield to biases in toxicity and efficacy measures.

Compliance with ethical standards

Conflict of interest. Both authors declare that they have no conflict of interest.

Ethical approval. This article does not contain any studies with human participants or animals performed by any of the authors.

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