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An Algorithm to Define the Optimum Biological Dose of Metronomic Chemotherapy

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Summary

The best effective dose of a chemotherapy is defined using the maximum tolerated dose (MTD) of toxicity. It is possible that the toxicity of a dose may increase when the dose-response curve is not monotonic. In the case of metronomic chemotherapy (MC) a $1/10^{th}$ level of MC dose is considered as a targeted dose of therapy and is safer in terms of toxicity levels. The objective of this study is to develop an algorithm based on the dose response model of MC to evaluate the best effective dose based on the molecular target agent. The molecular target agent is defined as the optimal biological dose achieved by the best effective dose, as the lowest dose with the highest rate of safety and efficacy. The first proposed design is parametric and assumes a logistic dose-efficacy curve for dose determination, and the second design uses quadratic regression to identify the optimal biological dose. We conducted extensive simulation studies to investigate the operating characteristics of the proposed designs. Simulation studies provide a possible way to decide on the best effective dose of MC to be considered in further phases through the finding of the optimal biological dose. The proposed design is assumed, with the threshold value of optimum biological dose (OBD), to detect the best dose of MC. This consistent design with specific dose response models can be recommended for practice.

Key words: OBD, bayesian algorithm, metronomic, MTD, CEC

1. Introduction

The maximum tolerated dose (MTD) is defined as the maximum dose of a drug to produce the desired therapeutic effect with acceptable side effects.

It is assumed that an increase of dose proportionally affects the tumor response. Traditionally, one level below the approved dose in a phase 1 study is considered a suitable dose to be carried over to the phase 2 study (Skipper et al., 1970; DeVita et al., 2008; Briasoulis et al., 2009). There is a certain chance of occurrence of chemo-resistant clones and impaired Quality of Life (QOL) due to the effect of conventional chemotherapy (Schmid et al., 2005; Golfinopoulos et al., 2007; Saltz, 2008). Metronomic Chemotherapy (MC) is an alternative choice to overcome the side effects as regards QOL and the occurrence of chemo-resistant clones. It is administered as a subtoxic dose (i.e. nearly $\frac{1}{10}^{th}$ of MTD) of some chemotherapy drugs for long periods to target angiogenesis (Hanahan et al., 2000; Kerbel et al., 2002; Kerbel and Kamen, 2004; Scharovsky et al., 2009).

MC is defined as next-generation chemotherapy (Pantziarka et al., 2016). A novel approach has been proposed to define the OBD in MC therapy (Bhattacharjee and Patil, 2017). There has also been an attempt to find the optimum biological dose in MC by time-dependent ROC (Bhattacharjee and Patil, 2016). The effect of a specific metronomic chemotherapy dose can be observed through the target Circulating Endothelial Cell (CEC) value. The effect on the CEC is restricted to an antiangiogenic window in tumor cell line studies (Skipper et al., 1970; Hobson and Denekamp, 1984; Vacca et al., 1999). In cell line studies of tumors, a specific dose level of drug is induced to initiate the antiangiogenic effect at a low dose level, and it is progressed up to an upper dose level. It is found that dose levels above and below the specific dose do not exert an antiangiogenic effect. The scientific objective is to establish the optimal biological dose (OBD) of MC to obtain the maximum CEC inhibiting effect. This inhibiting effect can be measured through repeatedly observed data and can be represented through a surrogate marker of angiogenesis (Marmé et al., 2007). Further, the CEC inhibiting effect can progress through the recurrence of tumor and death of the patient. The challenge is to establish the OBD of MC obtained through the CEC marker value for angiogenesis and thereafter progressed further with a time-to-event rate to the treated patients having a specific MC dose.

2. Generating the dataset

There is no consensus on the most appropriate approach to surrogate marker response with effective metronomic chemotherapy. Therefore a simulation study was performed to assess the OBD for the performance of MC. Datasets

were generated to resemble the skewed distributions seen in a motivating example of head and neck cancer (HNC). The CEC count is considered as a time-dependent surrogate marker. The baseline CEC count in the blood of HNC patients was taken from a normal distribution (with mean 114 CEC per ml; SD 15)(Ilie et al., 2014) for a total of 220 patients. Data is generated with four different choices of dose, denoted as dose 1, dose 2, dose 3 and dose 4. However, it is possible to consider several doses and obtain the best-performing optimum dose based on the controlled level of the surrogate marker (CEC). The IDs of the 220 patients were randomly assigned to dose 1, dose 2, dose 3 and dose 4 with metronomic chemotherapy from a binomial distribution. The baseline measurement of four covariates named ECOG (coded 0 and 1), Death Status (Yes or No), Tumor Size (mean 4.0 cm, SD 2) and Histological Grade (good, moderate and poor) were generated randomly for all 220 patients and merged using an Excel sheet. The ECOG, Death Status and Histological Grade were generated from binomial and multinomial distributions respectively. The baseline tumor sizes were obtained from a normal distribution. Further, the five follow-up visit observations for CEC and tumor size were assumed to have normal distribution. The mean CEC values at time points t_1, t_2, t_3, t_4, t_5 were assigned with mean 124, 128, 135, 126 and 120 respectively. The SD (15) was considered for each time point of CEC values to be generated as random measurements. The tumor size was assigned with mean $4.0, 3.4, 3.2, 3.0, 3.2$ with SD (2) for the time points $t_1, t_2, t_3, t_4,$ and t_5 respectively [Figure 1-3]. The continuous covariates were assumed to have a linear effect on the log relative hazard.

An exponential distribution with a hazard rate of 0.0003 was considered to generate the uncensored survival duration. It is approximated by the hazard rate in the HNC (Patil et al., 2015). The censored duration was also generated from the exponential distribution with a hazard rate of 0.0003 with approximately 45% censored observations. The required survival duration was defined for each case as the minimum of the uncensored and censored survival duration, and the event status defined accordingly. Recurrence is considered as the event of interest. The survival duration is represented as progression-free survival (PFS). The changes in survival duration as a treatment effect are given in Figure 4. Table 1 shows the results of Kaplan–Meier estimates.

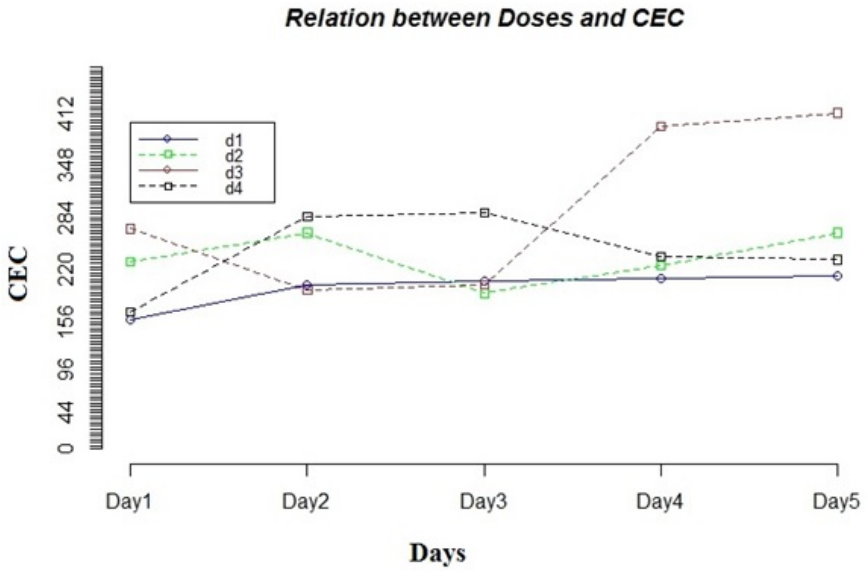

Figure 1. Doses with CEC

Table 1. Median estimates of duration of survival on different doses

Doses	number at risk	events	median	0.95LCL	0.95UCL
d_1	249	139	50	43	58
d_2	246	130	53	49	64
d_3	246	135	49	41	57
d_4	236	122	48	42	57

3. Toxicity monitoring

The specific metronomic dose is defined as d_j from a set of doses $(d_1, ..., d_J)$. A total number of n_j patients are initially exposed to dose level $'j'$. Any metronomic dose is sufficient to control for toxicity level. In any metronomic dose selection the toxicity is not the concern; only efficacy is to be considered to identify the best effective dose. The best effective dose is defined as the dose able to control the optimum level of the surrogate marker value or level as desired to arrest the tumor growth. Let the occurrence of toxicity be defined to have probability q_j for the specific dose level d_j. Further, a total of x_j patients experience toxicity occurrence for the specific dose d_j. The prior assumption of toxicity count for dose level d_j is defined as

$$x_j \sim \text{binom}(n_j, q_j). \tag{1}$$

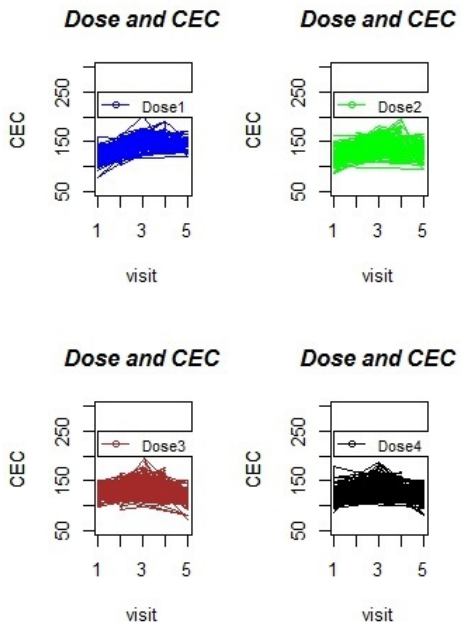

Figure 2. CEC changes over the visits

The prior assumption of probability q_j is defined as

$$q_j \sim \text{beta}(a, b). \tag{2}$$

Here, a and b are the hyperparameters. The upper range of toxicity that is acceptable is defined as ϕ. The total number of patients exposed to dose level j is η_j, and the number of patients experiencing toxicity at dose level j is x_j. The posterior probability $\Pr(q_j > \phi|\eta_j, x_j)$ can be considered to check the performance of dose level d_j in terms of toxicity. The set A of different doses is defined as

$$A = \{j : \bar{Pr}(q_j > \phi|\eta_j, x_j) < C_\tau, j = 1, \ldots, J\}. \tag{3}$$

The term C_τ is defined as a pre-specified toxicity dose level as a threshold value. The above equation is considered to protect patients from overtoxic doses. The small priori assumption of a, b is linked to the threshold value by $\text{Beta}(\phi; a, b) = 1 - C_\tau + \delta$. The term δ can be taken to be a very small positive number such as 0.05. In this work the models are defined as Model 1 and Model 2. Model 1 is defined under the classification as a Logistic Design, and Model 2 is defined as a Dose Response Model.

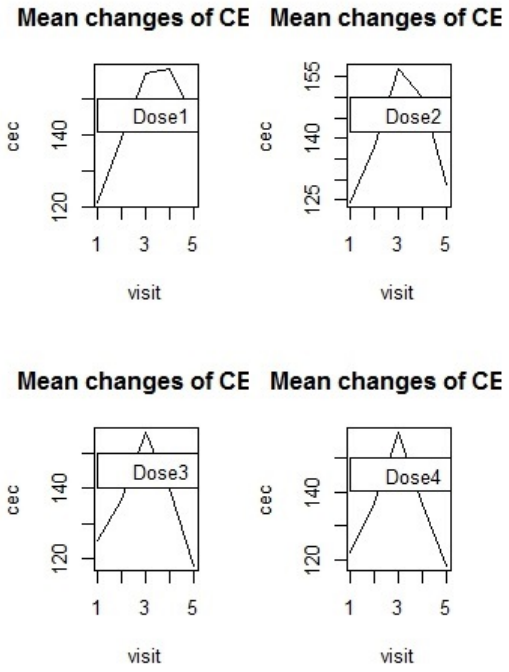

Figure 3. Mean CEC changes over the visits

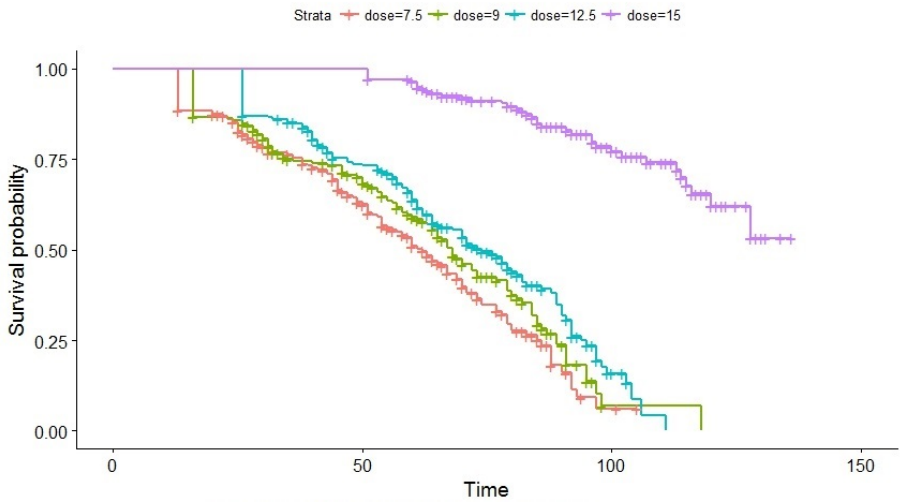

Figure 4. Kaplan–Meier curves on doses

3.1. Logistic response models

The OBD is defined as a success if it maintains the CEC level within certain limits, and otherwise not. It is further defined as success or failure in terms of probability through the consideration of binomial data. The probability of success of dose d_j is defined as p_j, with the function

$$g(p_j) = \beta_1 + \beta_2 d_j. \tag{4}$$

The OBD threshold value is defined as the function $f(s)$ with uniform distribution on $[c_1, c_2]$

$$f(s) = \begin{cases} \frac{1}{c_2 - c_1} & \text{if } c_1 \leqslant s \leqslant c_2; \\ 0 & \text{if otherwise.} \end{cases}$$

The corresponding cumulative dose is defined using p_j as

$$p_j = \int_{c_1}^{d_j} f(s)ds = \frac{d_j - c_1}{c_2 - c_1} \text{ for } c_1 \leqslant d_j \leqslant c_2. \tag{5}$$

Equation (5) helps us to identify $p_j = \beta_1 + \beta_2 d_j$, where $\beta_1 = \frac{-c_1}{c_2 - c_1}$ and $\beta_2 = \frac{1}{c_2 - c_1}$.
The OBD threshold value is defined as $c_1 \leqslant d_j \leqslant c_2$. The term p_j is taken with normal distribution as

$$p_j = \frac{1}{2\pi} \int_{-\infty}^{x} \exp[-\frac{1}{2}(\frac{s - \mu}{sigma})^2]ds, \quad \Phi \sim N(0, 1), \tag{6}$$

$$\Phi^{-1}(p_j) = \beta_1 + \beta_2 d_j, \tag{7}$$

where $\beta_1 = -\mu/\sigma$ and $\beta_2 = 1/\sigma$. The link function g is adopted with the inverse cumulative normal probability function Φ^{-1}.

The OBD function is defined as

$$f(s) = \frac{\beta_2 \exp(\beta_1 + \beta_2 s)}{[1 + \exp(\beta_1 + \beta_2 s)]^2}, \tag{8}$$

hence

$$p_j = \int_{-\infty}^{x} f(s)ds = \frac{exp(\beta_1 + \beta_2 d_j)}{[1 + exp(\beta_1 + \beta_2 d_j)]}. \tag{9}$$

The link function is considered as

$$\log(\frac{p_j}{1-p_j}) = \beta_1 + \beta_2 d_j. \tag{10}$$

The distribution of extreme value is

$$f(s) = \beta_2 \exp[(\beta_1 + \beta_2 s) - \exp(\beta_1 + \beta_2 s)] \tag{11}$$

and the OBD distribution is defined as $p_j = 1 - \exp[-\exp(\beta_1 + \beta_2 d_j)]$, log[-log$(1-p_j)$] $= \beta_1 + \beta_2 d_j$. The link log[-log$(1-p_j)$] is defined as the complementary of the log-log function. The specific dose d_j and corresponding CEC levels observed with different doses are plotted in Figure 1. Let us assume that the OBD is given as $p_j = \frac{y_i}{n_i}$. The dose is defined as d and different doses are labeled as d_j. The total number of patients treated with dose d_j is n_i, and the number of patients observed with controlled OBD is defined as y_i. Now the probability of success due to dose d_j is p_i. The model is defined as

$$p_j = \frac{\exp(\beta_1 + \beta_2 d_j)}{1 + \exp(\beta_1 + \beta_2 d_j)}, \tag{12}$$

$$\log(\frac{p_j}{1-p_j}) = \beta_1 + \beta_2 d_j, \tag{13}$$

$$\log(1 - p_j) = -\log[1 + \exp(\beta_1 + \beta_2 d_j)]. \tag{14}$$

The log-likelihood function with total sample size N is defined as

$$l = \sum_{i=1}^{N} [y_i(\beta_1 + \beta_2 d_j) - n_i \log[1 + \exp\ (\beta_1 + \beta_2 d_j)] + \log(\tbinom{n_i}{y_i}), \tag{15}$$

$$U_1 = \frac{\delta l}{\delta \beta_1} = \sum \{y_i - n_i [\frac{\exp(\beta_1 + \beta_2 d_i)}{1 + \exp(\beta_1 + \beta_2 d_i)}]\} = \sum (y_i - n_i p_j), \tag{16}$$

$$U_2 = \frac{\delta l}{\delta \beta_2} = \sum \{y_i d_j - n_i d_j [\frac{\exp(\beta_1 + \beta_2 d_j)}{1 + \ \exp(\beta_1 + \beta_2 d_j)}]\}, \tag{17}$$

$$U_2 = \sum (y_i - n_i p_j) = \sum d_j (y_i - n_i p_j). \tag{18}$$

The information matrix is defined as

$$T = \begin{vmatrix} \sum n_i p_j(1-p_j) & \sum n_i d_j p_j(1-p_j) \\ \sum n_i d_j p_j(1-p_j) & \sum n_i d_j^2 p_j(1-p_j) \end{vmatrix}.$$

The maximum likelihood estimates are defined as

$$T^{(m-1)} b^m = I^{(m-1)} b^{(m-1)} + U^{(m-1)}. \tag{19}$$

The number of the approximation is defined as (m), and the vector of estimates is given as b with the deviance function as

$$D = 2 \sum_{i=1}^{N} [y_i \log(\frac{y_i}{\hat{y}_i}) + (n_i - y_i) \log(\frac{n_i - y_i}{n_i - \hat{y}_i})]. \tag{20}$$

Dose selection algorithm: The proposed method will serve to decide the best optimum dose through the following steps:
(I) It will begin with a low dose level l to treat a small number of patients (a cohort) and simultaneously cover all types of possible dose levels in different cohorts.
(II) The definition of toxicity for different dose levels j will be considered with equation (3) to cover safety issues.
(III) The outcome based on the level of efficacy at the dose level $l-1$ will be computed using the credible intervals and posterior probability distribution with $\Pr(\beta > 0|d_j)$. The dose level may be escalated to $j+1$ provided $\Pr(\beta > 0|d_j) > C_{E1}$, otherwise the dose level will remain at j. If $\Pr(\beta > 0|d_j) < C_{E2}$, the dose level may be de-escalated to $j-1$.
(IV)The next step will be to cover the maximum sample size. Once it is reached, then based on comparisons between different efficacy levels the best effective dose will be defined as the optimum biological dose of metronomic chemotherapy. It is crucial to take a decision between the best effective dose j and $j+1$ to obtain the maximum of the dose-efficacy using $\Pr(\beta > 0|d_{j+1}) < C_{E2}$. The best dose will be determined by the maximum peak of the curve reached by the dose levels. The best value can be decided through calibration between C_{E1} and C_{E2}.

3.2. Quadratic logistic design

The status of the dose efficacy is defined with dichotomous categories. The probability of efficacy of dose level j is defined as p_j. It has been observed

that the CEC value after metronomic chemotherapy is not monotonic. The logistic regression curve, with consideration of the quadratic form, is taken for the values of CEC changes from metronomic chemotherapy. The equation is defined as

$$\log(\frac{p_j}{1-p_j}) = \alpha + \beta d_j + \gamma d_j^2, j = 1, 2, \ldots, J. \tag{21}$$

The specific dose d_j is found to be effective among γ_j patients out of η_j treated patients with $p_j = \frac{\gamma_j}{\eta_j}$. The likelihood function is defined as $D = \{y_j, \eta_j; j = 1, ..., J\}$ with

$$L(D|\alpha, \beta, \gamma) \propto \prod_{j=1}^{J} (\frac{e^{\alpha+\beta d_j+\gamma d_j^2}}{1+e^{\alpha+\beta d_j+\gamma d_j^2}})^{\gamma_j} (\frac{1}{1+e^{\alpha+\beta d_j+\gamma d_j^2}})^{\eta_i-\gamma_i} \tag{22}$$

The posterior estimates of the regression parameters are defined as α, β, and γ with $f(\alpha, \beta, \gamma|D) \propto f(\alpha, \beta, \gamma)$ where $f(\alpha, \beta, \gamma)$ is the prior distribution of α, β, γ. The posterior estimates of the samples were obtained through the Markov Chain Monte Carlo (MCMC) method. The prior assumptions for α are taken to have Cauchy(0,10) distribution. The prior assumptions of β and γ are considered as Cauchy(0,2.5).

Dose selection algorithm: The proposed method can be described as follows:
(I) Start with the lowest metronomic dose d_1 based on the experience of the medical oncologist.
(II) The probability terms will be considered to initiate the dose level j through consideration of toxicity levels of the acceptable set of doses A.
(III) The posterior mean estimate of the observed higher value of efficacy will be considered for the acceptable set A. The dose can be increased to $j+1$ if $j^* > j$, otherwise not. If $j^* < j$ the dose level will remain at j.
(IV) The dose will be defined as the optimal biological dose once the highest estimate of the efficacy level is reached.
(V) A parametric model is used to perform the analysis.

4. Results

The results obtained using the different probabilities for Model 1 and Model 2 are given in Table 2. The proportions of the patients considered for the different doses during the simulation studies are detailed in Table 3. The

corresponding generated selected probabilities for all doses are also given in Table 3.

Table 2. Posterior estimates of the models through measurement of surrogate marker

Model	Parameter	Posterior Mean	SD	HPD	DIC
Model1	β_1	332.2	74.81	(216.9,450.1)	253.2
	β_2	-8.182	6.47	(18.56,1.942)	
	σ_1	67.19	12.21	(48.25,95.6)	
	τ_1	0.00024	0.00008	(0.0001,0.0004)	
Model2	α	679.0	2621.0	(-604.6, 10660.0)	226.4
	β	-74.28	502.5	(-1983.0, 170.8)	
	γ	2.923	22.45	(-7.975, 87.25)	
	σ_2	74.66	28.77	(47.66, 179.7)	
	τ_2	0.00021	0.00010	(0.00025,0.00043)	

Table 3. Performance of methods through measurement of surrogate marker

		Dose				
Scenario	Characteristics	d_1	d_2	d_3	d_4	Overtoxic
Scenario 1:	Selected Probability	0.01	0.10	0.20	0.69	0
	Proportion of Patients	0.08	0.19	0.1	0.63	
Scenario 2:	Selected Probability	0.12	0.15	0.23	0.50	0
	Proportion of Patients	0.18	0.22	0.09	0.51	
Scenario 3:	Selected Probability	0.21	0.27	0.15	0.37	0.01
	Proportion of Patients	0.35	0.29	0.04	0.32	
Scenario 4:	Selected Probability	0.29	0.43	0.18	0.10	0
	Proportion of Patients	0.49	0.31	0.1	0.10	

The arrangements of different doses with different probabilities are named Scenario 1, Scenario 2, Scenario 3 and Scenario 4 respectively. It is shown that an overtoxic dose was generated only in Scenario 3. However, this was a very low level of overtoxic dose. Our work is presented using simulation studies. It is important to consider the quality of the surrogate marker through the posterior probability of efficacy E and safety S. Let us assume that the marginal posterior probabilities of the associated parameters are (σ_2 or τ_2) for S and E respectively.

The relation between S and E is defined as $\Pr(S = 1) = \mathrm{V} * \Pr(E = 1)$. If $\mathrm{V} = 1$ then it is expected that the OBD is a good marker; otherwise, if $\mathrm{V} > 1$ then OBD is not a good marker. In this setting the parameters σ and τ provide a strong relation between S and E. The prior assumptions for S and E are provided by σ and τ. The values of σ_1 and τ_1 become related

when E is appreciated through consideration of S. When σ_1 and τ_1 are not related then E may be ignored and corresponding doses may be avoided.

Equations (10) and (20) are considered as Model 1 and Model 2 respectively. The additive parameters σ and τ defined as σ_1 and τ_1 for Model 1 and σ_2 and τ_2 for Model 2 are considered. The simulation is conducted using different values of $\sigma_1, \tau_1, \sigma_2$ and τ_2 respectively. The simulations are conducted over 20,000 iterations with a 1000-iteration burn-in period for each chain. The convergence of the statistics was observed through simulation techniques. The posterior credible intervals are provided in Table 2. The iteration process was stopped by observing the converged trace plots for each parameter of the models. The quadratic logistic model is found more suitable to be considered based on the minimum DIC value.

5. Discussion

Our proposed method may bridge the gap between requirements and the availability of a statistical tool to determine the optimum dose of metronomic chemotherapy. It is important to consider surrogate efficacy data as an alternative to efficacy to make quick decisions about dose efficacy. The surrogate marker also needs to be strong enough to represent an alternative efficient marker(Kumar et al., 2017). In this proposed method, a higher marginal probability for the surrogate marker is considered to represent the reality. The performance of the surrogate marker represents the path to decide the OBD. It is expected that this proposed method can reduce the mean squared error and improve performance in terms of accuracy. A limitation of this method is that the prior information of the surrogate endpoints is ignored. This work is based on the performance of one surrogate marker with the aim of finding the OBD. However, it can be extended through simultaneous consideration of the performance of multiple surrogate markers. It is a limitation of this work that only one surrogate marker is considered. An attempt has been made to use measurement of toxicity and efficacy to deal with time-to-event through CRM to facilitate multiple outcomes (Cheung and Chappell, 2000).

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Appendix

```
Model1
model
{
for (i in 1:20)
{
mu.dmf[i] <- beta1 + beta2*fl[i]
dmf[i] ~ dnorm(mu.dmf[i],tau)
}
beta1 ~ dnorm(0.0,0.000001)
beta2 ~ dnorm(0.0,0.000001)
sigma1 ~ dunif(0,400)
tau1 <- 1/(sigma1*sigma1)
for (i in 1:20)
{ # calculate residuals
residual[i] <- dmf[i] - mu.dmf[i]
}
pred.mean.1.7 <- beta1 + beta2*1.7
pred.ind.1.7 ~ dnorm(pred.mean.1.7, tau1)
}
```

```
\noindent
Model2
model {
for (i in 1:20)
{
mu.dmf[i] <- alpha + beta*fl[i] + gamma*fl[i]*fl[i]
# regression equation
dmf[i] ~ dnorm(mu.dmf[i],tau)
# distribution individual values
}
alpha ~ dnorm(0.0, 0.000001)
beta  ~ dnorm(0.0, 0.000001)
gamma ~ dnorm(0.0, 0.000001)
sigma2 ~ dunif(0,200)
tau2 <- 1/(sigma2*sigma2)
for (i in 1:20)
{ # calculate residuals
residual[i] <- dmf[i] - mu.dmf[i]
}
pred.mean.1.7 <- alpha + beta1*1.7 + beta2*1.7*1.7
# mean prediction for fl=1.7
pred.ind.1.7 ~ dnorm(pred.mean.1.7, tau2)
# individual pred for fl=1.7
}
```