A Bayesian Adaptive Design for Cancer Phase I Trials Using a Flexible Range of Doses

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Abstract

We present a Bayesian adaptive design for dose finding in cancer phase I clinical trials. The goal is to estimate the maximum tolerated dose (MTD) after possible modification of the dose range during the trial. Parametric models are used to describe the relationship between the dose and the probability of dose limiting toxicity (DLT). We investigate model reparameterization in terms of the probabilities of DLT at the minimum and maximum available doses at the start of the trial. Trial design proceeds using escalation with overdose control (EWOC), where at each stage of the trial, we seek the dose of the agent such that the posterior probability of exceeding the MTD of this agent is bounded by a feasibility bound. At any time during the trial, we test whether the MTD is below or above the minimum and maximum doses, respectively. If during the trial, there is evidence that the MTD is outside the range of doses, we extend the range of doses and complete the trial with the planned sample size. At the end of the trial, a Bayes estimate of the MTD is proposed. We evaluate design operating characteristics in terms of safety of the trial design and efficiency of the MTD estimate. The methodology is further compared to the original EWOC design.

Key Words: Cancer phase I trials; Maximum tolerated dose; Escalation with overdose control; Dose limiting toxicity; Continuous dose; Flexible dose range.

1. Introduction

Cancer phase I clinical trials are small sequential studies designed to investigate the safety and tolerability of investigational new agents or combination of existing cytotoxic and/or biologic agents. These trials enroll late stage patients who have exhausted all standard therapy [1]. The primary objective of these trials is to estimate a dose level that is associated with a predetermined level of dose limiting toxicity (DLT). Such a dose is referred to as the maximum tolerated dose (MTD) or phase II dose. A review of single agent dose-finding designs can be found in [2-4].

Existing statistical designs such as the continual reassessment method (CRM) [5-11] and escalation with overdose control (EWOC) [12-21] consist of searching for the MTD among a pre-determined set of discrete doses or within a bounded interval of doses specified by the clinicians. If the true MTD happens to be below the minimum dose

available in the trial X_{min}, then such designs lead to stopping the trial using some type of statistical or deterministic stopping rules. As a result, enrollment to the trial is either suspended and the clinical protocol is amended to expand the dose range or the trial is closed to enrollment. On the other hand, if the true MTD is above the maximum dose available in the trial X_{max}, these statistical designs and other algorithmic designs such as the standard '3+3' and its modifications [22-24] or acceleration titration design [22, 25] will usually proceed and enroll the planned number of patients in the trial and recommend the last dose as the phase II dose.

In this manuscript, we extend EWOC design by expanding the support of the prior density of the MTD to the interval $(0, \infty)$. Clinicians specify a range of available doses in the interval $[X_{min}, X_{max}]$ based on their prior belief or preliminary data about the safety of the dose X_{min} and the location of the true MTD in $[X_{min}, X_{max}]$. We next ask clinicians to specify a range of doses they are willing to expand below X_{min} if there is statistical evidence that X_{min} is too toxic. We further ask them to pre-specify a range of doses to be expanded beyond X_{max} if there is statistical evidence that the probability of DLT at X_{max} is way below the target probability of DLT. This approach will allow us to search for the MTD beyond $[X_{min}, X_{max}]$ without suspending accrual, stopping the trial, or recommending a suboptimal dose as the phase II dose. Moreover, design operating characteristics are carried out at the design stage of the trial and will take into account any dose range expansion below X_{min} or above X_{max}.

2. Model

2.1 Dose-Toxicity Model

Consider the problem of identifying a tolerable dose $x > 0$ of a cytotoxic agent. We consider the dose-toxicity model of the form

$$\text{Prob}(Y = 1 \mid x) = F(\beta_0 + \beta_1 x), \tag{2.1}$$

where Y is the indicator of dose limiting toxicity (DLT), $Y = 1$ if a patient given dose x exhibits DLT within one cycle of therapy, and $Y = 0$ otherwise, and F is a known cumulative distribution function. Let X_{min} and X_{max} be the minimum and maximum doses available in the trial.

We will assume that $\beta_1 > 0$ so that the probability of DLT increases with dose. The MTD is defined as the dose $\gamma > 0$ such that

$$\text{Prob}(Y = 1 \mid \gamma) = \theta. \tag{2.2}$$

The value of the target probability θ is pre-specified by the clinicians and depends on the nature and clinical manageability of the DLT; it is set relatively high when the DLT is a transient, reversible or non-fatal condition, and low when it is life threatening. It follows from (2.1) and (2.2) that

$$\gamma = \frac{F^{-1}(\theta) - \beta_0}{\beta_1}. \tag{2.3}$$

Suppose that the dose levels are standardized to be in the interval [0, 1] so that X_{min} corresponds to dose level 0 and X_{max} to dose level 1. We reparameterize model (2.1) in

terms of ρ_0, the probability of DLT at dose level 0, and ρ_1, the probability of DLT at dose level 1. This reparameterization is convenient to clinicians since prior information on ρ_0 and ρ_1 may be available from other trials. It can be shown that

$$\begin{cases} \beta_0 = F^{-1}(\rho_0) \\ \beta_1 = F^{-1}(\rho_1) - F^{-1}(\rho_0) \end{cases}. \tag{2.4}$$

The MTD in (2.3) becomes

$$\gamma = \frac{F^{-1}(\theta) - F^{-1}(\rho_0)}{F^{-1}(\rho_1) - F^{-1}(\rho_0)}. \tag{2.5}$$

Let $D_n = \{(x_i,y_i),\ i = 1, \ldots, n\}$ be the data after enrolling n patients in the trial. The likelihood function for the model parameters is

$$L(\rho_0, \rho_1 \mid D_n) = \prod_{i=1}^{n} \left(G(\rho_0, \rho_1; x_i)\right)^{y_i} \left(1 - G(\rho_0, \rho_1; x_i)\right)^{1-y_i}, \tag{2.6}$$

where

$$G(\rho_0, \rho_1; x_i) = F\left(F^{-1}(\rho_0) + \left[F^{-1}(\rho_1) - F^{-1}(\rho_0)\right] x_i\right). \tag{2.7}$$

2.2 Prior and Posterior Distributions

We assume that $\rho_1 \sim \text{beta}(a_1, b_1)$ and conditional on ρ_1, $\rho_0 / \rho_1 \sim \text{beta}(a_2, b_2)$. Under lack of prior information about these parameters, we take $a_i = b_i$, $i = 1, 2$. Using Bayes rule, the posterior distribution of the model parameters is

$$\pi(\rho_0, \rho_1 \mid D_n) \propto \prod_{i=1}^{n} \left(G(\rho_0, \rho_1; x_i)\right)^{y_i} \left(1 - G(\rho_0, \rho_1; x_i)\right)^{1-y_i} \pi(\rho_1)\pi(\rho_0 \mid \rho_1). \tag{2.8}$$

Features of this posterior distribution are estimated using WinBUGS[26] and JAGS.

2.3 Trial Design

The adaptive design uses the EWOC scheme where at each stage of the trial, the posterior probability of overdosing a future patient is bounded by a feasibility bound α. Furthermore, at each stage of the trial, we check whether or not the minimum dose $X_{\min}$ is likely to be too toxic and the maximum dose $X_{\max}$ is likely to be very safe. If either condition holds, the dose range is expanded accordingly. Let L be the largest amount of the drug the clinician is willing to expand from below in case $X_{\min}$ is too toxic and U be the largest amount to be added to $X_{\max}$ in case $X_{\max}$ is very safe.

1. The first patient (or cohort of m patients) receives dose $x_1 = X_{\min}$. Let $D_1 = \{(x_1, Y_1)\}$.

2. The second patient receives dose x_2 corresponding to the α-th percentile of $\pi(\gamma \mid D_1)$, the posterior distribution of the MTD given the data. In general, the i-th patient receives dose
   $x_i = \Pi^{-1}(\alpha \mid D_{i-1})\, I(X_{\min} < \Pi^{-1}(\alpha \mid D_{i-1}) < X_{\max}) + X_{\min}\, I(\Pi^{-1}(\alpha \mid D_{i-1}) \leq X_{\min}) + X_{\max}\, I(\Pi^{-1}(\alpha \mid D_{i-1}) \geq X_{\max})$.
3. For $i=1,\ldots,n-1$, if $P(P(\text{DLT} \mid x = X_{\min}) > \theta + \delta_1 \mid D_i) > \delta$, expand the range of doses to $[X_{\min} - L, X_{\max}]$ and patient $i+1$ receives the dose
   $x_{i+1} = \Pi^{-1}(\alpha \mid D_i)\, I(X_{\min} - L < \Pi^{-1}(\alpha \mid D_i) < X_{\max}) + (X_{\min} - L)\, I(\Pi^{-1}(\alpha \mid D_i) \leq X_{\min} - L) + X_{\max}\, I(\Pi^{-1}(\alpha \mid D_i) \geq X_{\max})$. If $P(P(\text{DLT} \mid x = X_{\max}) < \theta - \delta_2 \mid D_i) > \delta$, expand the range of doses to $[X_{\min}, X_{\max} + U]$ and patient $i+1$ receives the dose
   $x_{i+1} = \Pi^{-1}(\alpha \mid D_i)\, I(X_{\min} < \Pi^{-1}(\alpha \mid D_i) < X_{\max} + U) + X_{\min}\, I(\Pi^{-1}(\alpha \mid D_i) \leq X_{\min}) + (X_{\max} + U)\, I(\Pi^{-1}(\alpha \mid D_i) \geq X_{\max} + U)$.
4. Repeat steps 2 and 3 until n patients are enrolled to the trial.

Here, $\Pi^{-1}(\cdot \mid D_{i-1})$ denote the inverse cumulative distribution function of the posterior distribution of the MTD γ given the data D_{i-1}. At the end of the trial, we estimate the MTD as the median of the posterior distribution $\pi(\gamma \mid D_n)$. Step 2 of the algorithm states that the dose allocated to the i-th patient is $\Pi^{-1}(\alpha \mid D_{i-1})$ provided that this dose is within the range of doses available in the trial. Otherwise, the dose allocated to the i-th patent is either $X_{\min}$ or $X_{\max}$ depending on whether $\Pi^{-1}(\alpha \mid D_{i-1})$ is below the minimum dose or above the maximum dose available in the trial. Step 3 states that anytime during the trial, if there is evidence that either the minimum dose is likely to be to toxic or the maximum doses is likely to have a probability of DLT below the target θ, then the dose range is expanded either below $X_{\min}$ or above $X_{\max}$ and dose allocation proceeds as in step 2 with this expanded range of doses.

δ_1, δ_2, and δ are design parameters and are selected to produce good design operating characteristics. L and U control the size of the dose range expansion and are pre-specified by the clinicians. The parameter α is the feasibility bound and controls the probability of overdosing patients. It is set at 0.1 at the onset of the trial, and then increases by increments of 0.05 to a maximum value of 0.5 after each patient is enrolled to the trial. In the simulation results we studied, the parameters associated with the expansion rules are $\delta_1 = \delta_2 = 0$ and $\delta = 0.8$.

The possibility of modifying the range of doses during the trial is very useful to clinicians and can help salvage a trial that shows a high rate of DLT around the minimum dose or a low rate of DLTs around the maximum dose. In such cases, the proposed design expands the range of doses without suspending enrollment to the trial or amending the clinical protocol since the design operating characteristics are performed at the design stage of the trial.

3. Simulation Studies

3.1 Simulation Set-up and Scenarios

We studied the performance of this design by simulating m = 1000 trials under three scenarios of the true MTD using the logistic function $F(u) = (1 + e^{-u})^{-1}$ as the true and working model. In all cases, the target probability of DLT is θ = 0.33, planned trial sample size is n = 30 patients, and $a_j = b_j = 1$, j = 1, 2 which corresponds to vague priors for ρ_0 and ρ_1. For a hypothetical trial, we took $X_{\min}$ = 100 mg/m^2 and $X_{\max}$ = 500 mg/m^2, L = 100 mg/m^2, U = 200 mg/m^2 and the following scenarios for the true MTD, γ = 37 mg/m^2, 308 mg/m^2, and 586 mg/m^2. The doses are standardized to the interval [0, 1] and the true standardized MTDs are −0.15, 0.52, and 1.21. The corresponding true model parameters are (ρ_0, ρ_1) = (0.45, 0.95), (0.05, 0.8), and (0.01, 0.2). We compared the safety of a trial and efficiency of the estimated MTD between the following 3 designs, (1) Dose expansion (DE) design: this is the proposed design where an expansion rule is put in place and the range of doses is expanded if needed, (2) No dose expansion (NDE) design: this design uses the stopping rule but does not expand the range of doses, and (3) No stopping rule (NS): this design does not use a statistical stopping rule as in the original EWOC.

Safety of each design is assessed by computing the average percent of DLTs

$$ave_{\text{DLT}} = 1/(m \cdot n) \cdot \sum_{i=1}^{m} \sum_{j=1}^{n} I(Y_{i,j} = 1), \tag{3.1}$$

and the percent of trials that have a DLT rate exceeding $\theta + \delta$, for δ = 0.05, 0.1,

$$\%\text{trials w. high DLT rate } = m^{-1} \cdot \sum_{i=1}^{m} \left\{ I\left(n^{-1} \sum_{j=1}^{n} Y_{i,j} > \theta + \delta \right) \right\}. \tag{3.2}$$

The threshold θ + 0.1 is usually considered to be an indication of an excessive DLT rate. Efficiency of the trial is evaluated by calculating the average bias

$$ave_{\text{bias}} = m^{-1} \cdot \sum_{i=1}^{m} (\hat{\gamma}_i - \gamma_{\text{true}}), \tag{3.3}$$

where $\hat{\gamma}_i$ is the estimate of the MTD for the i-th trial and γ_{true} is the true MTD under a particular scenario, the root mean square error

$$\text{RMSE} = \left(m^{-1} \cdot \sum_{i=1}^{m} (\hat{\gamma}_i - \gamma_{\text{true}})^2 \right)^{1/2}, \tag{3.4}$$

the percent of trials with estimated MTD within (100×p)% of the dose range of the true MTD, 0 < p < 1,

$$\%\text{recom } 1 = m^{-1} \cdot \sum_{i=1}^{m} I\left(\gamma_{\text{true}} - p(X_{\max} - X_{\min}) \le \hat{\gamma}_i \le \gamma_{\text{true}} + p(X_{\max} - X_{\min}) \right), \tag{3.5}$$

and the percent of trials with estimated MTD within (100×p)% of the value of the true MTD, 0 < p < 1,

$$\%\text{recom } 2 = m^{-1} \cdot \sum_{i=1}^{m} I\left(\gamma_{\text{true}} - p\gamma_{\text{true}} \le \hat{\gamma}_i \le \gamma_{\text{true}} + p\gamma_{\text{true}}\right). \quad (3.6)$$

The statistics in (3.5) and (3.6) can be interpreted as the percent of MTD recommendation within a neighborhood of the true MTD. They differ with respect to the structure of this neighborhood. In (3.5), the width of the tolerance interval is a fraction of the dose range and is constant regardless of the value of γ_{true}, see [18]. In (3.6), the width of the tolerance interval is a fraction of γ_{true} so that wider intervals are tolerated for high values of γ_{true} and tighter neighborhoods are imposed for values of γ_{true} near the minimum dose $X_{\min}$. Such a statistic was used for single agent dose finding trials in [27] and dose combination trials in [28].

3.2 Results

Table 1 gives the probability of expanding the dose range under the three scenarios along with the median trial sample size and 90% confidence interval. When the true MTD is below the minimum dose $X_{\min}$, the probability of expanding the dose range from below is 0.81 with a median sample size of 13. The probability of expanding the dose range from above is 0.96 when the true MTD is above the maximum dose $X_{\max}$ and the corresponding median sample size is 6.

Table 1. Probability of expanding dose range and CI for sample size n

	True MTD		
	−0.15	**0.52**	**1.21**
P(expand)	0.81	0.048	0.96
Median n	13	30	6
90% CI for n	[4, 30]	[30,30]	[6,26]

3.2.1 Trial Safety

Table 2 shows that when the true MTD is below the minimum dose available in the trial, the average percent of DLTs computed using (3.1) is lower using the proposed design (DE) relative to a design where no stopping rule is used (NS) or the design that stops the trial but does not expand the range of doses (NDE). When the true MTD is in the middle of the dose range, the average percent of DLTs is close to the target probability of DLT θ = 0.33 for all 3 designs. In the case where the true MTD is above $X_{\max}$, ave_{DLT} using design DE is much closer to the target $\theta = 0.33$ than the other two designs. The high DLT rate of 45.9% using DE is probably due to the fact that a much higher rate of DLT is observed prior to the dose range expansion from below. The same conclusion holds for the percent of trials with an excessive DLT rate. When the true MTD is either in the middle of the dose range or above $X_{\max}$, the percent of trials with DLT rate exceeding θ computed using (3.2) is very small. When the true MTD is below $X_{\min}$, this percent is lower using design DE relative to the other two designs, but is still high. Again, this is due to the fact that the median sample size before expanding the dose range is 13.

3.2.2 Trial Efficiency

Table 2 shows that the average bias of the estimate of the MTD computed using (3.3) is always lower when using the proposed design DE relative to the other two designs when the true MTD is outside the range of doses available in the trial. When the true MTD is in the middle of the dose range, the average bias is very small, similar to the NS design. Similar conclusions hold for the RMSE computed using (3.4). Similarly, the percent of

Table 2. Operating Characteristics comparing the three designs

		True MTD								
		−0.15			0.52			1.21		
Design		DE	NDE	NS	DE	NDE	NS	DE	NDE	NS
Safety	Average % DLTs	45.9	56.1	48.6	34.1	32.3	34.0	28.2	4.7	16.6
	% trials w. DLT rate > θ + 0.1	79.0	92.7	84.8	4.7	3.6	4.7	0.1	0.0	0.0
Efficiency	Average MTD	−0.057	0.017	0.012	0.518	0.542	0.521	1.212	0.999	0.996
	Average bias	0.099	0.174	0.169	−0.001	0.022	0.001	−0.004	−0.217	−0.220
	Root MSE	0.128	0.178	0.172	0.105	0.148	0.097	0.150	0.218	0.221
% trials with MTD estimate in	(γ − 0.10, γ + 0.10)	0.567	0.0	0.0	0.663	0.624	0.713	0.494	0.0	0.0
	(γ − 0.15, γ + 0.15)	0.729	0.0	0.0	0.848	0.799	0.886	0.672	0.0	0.0
	(γ − 0.15γ, γ + 0.15γ)	0.163	0.0	0.0	0.550	0.534	0.589	0.745	0.0	0.0
	(γ − 0.20γ, γ + 0.20γ)	0.21	0.0	0.0	0.685	0.643	0.731	0.878	0.99	0.96

trials with estimated MTD in a neighborhood of the true MTD as measured by (3.5, 3.6) is almost always higher when using design DE relative to the other two designs when the true MTD is outside the range of doses. When the true MTD is in the middle of the dose range, design NS does better than design DE with an excess of 4 to 5% in the percent of trials with MTD estimate within a given neighborhood of the true MTD. Based on these results, we conclude that the method is useful in estimating the MTD efficiently and is an improvement over the original EWOC design in the case where the true MTD turns out to be outside the range of doses available in the trial.

4. Discussion

We described a dose finding design for cancer phase I clinical trials which uses a flexible dose range. In this design, clinicians propose a dose range $[X_{\min}, X_{\max}]$ for searching for the MTD with the flexibility to expand this range to $[X_{\min} - L, X_{\max} + U]$ if there is statistical evidence that the lowest dose is too toxic or the largest dose level is too safe. The approach is an extension of the method described in [12] and is more general than the extension described in [15]. When there is evidence that the lowest dose is too toxic or the highest dose has a low probability of DLT, the method has several advantages over previous approaches. For instance, there is no need to suspend accrual, amend the clinical protocol, or close the trial since the consequences of expanding the dose range are evaluated using the design operating characteristics at the design stage of the trial.

We assessed the performance of the approach using three scenarios for the true MTD and by comparing the proposed design with a design that does not expand the range of doses and a design that does not use a statistical stopping rule as in the original EWOC. We showed that our method is safer and can estimate the MTD more efficiently. We plan to further study the operating characteristics by considering more scenarios, model misspecification, and compare the safety of the trial and efficiency of the estimate of the

MTD with the design that uses $[X_{\min} - L, X_{\max} + U]$ as the initial dose range. We further plan to adapt this method to the CRM for both continuous and discrete set of doses.

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