A Bayesian Adaptive Design in Cancer Phase I Trials using Dose Combinations with Ordinal Toxicity Grades

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Abstract

We propose a Bayesian adaptive design for early phase drug combination cancer trials incorporating ordinal grade of toxicities. Parametric models are used to describe the relationship between the dose combinations and the probabilities of the ordinal toxicities under the proportional odds assumption. Trial design proceeds by treating cohorts of two patients simultaneously using Escalation With Overdose Control (EWOC) and Continual Reassessment Method (CRM). At the end of the trial, we estimate the MTD curves as a function of Bayes estimates of the model parameters. We evaluate design operating characteristics in terms of safety of the trial and percent of dose recommendation at dose combination neighborhoods around the true MTD by comparing this design to the one that uses a binary indicator of DLT.

1. Introduction

Cancer phase I clinical trials are sequential designs enrolling late stage cancer patients who have exhausted standard treatment therapies. [1] The primary aim of a phase I trial is to estimate the maximum tolerated dose (MTD) of a new drug or combination of drugs for future efficacy evaluation in phase II/III trials. The estimation of the MTD is guided by the occurrence of dose-limiting toxicities (DLT) that are pre-specified adverse events classified as grade 3 or higher, based on common toxicity criteria for adverse events (CTCAE) [2].

CTCAE are international guidelines that measure the severity of an adverse event from mild (grade 1) to death related (grade 5). Most of the phase I clinical trials dichotomizes DLT as 0-2 (absence) and 3-5 (presence) entailing lost of information in the sense that the dose escalation algorithm should proceeds more cautiously when a grade 2 toxicity is observed instead of grade 1 or no toxicity.

There are several methodologies [3–16] taking into account all grades and types of toxicities for a single agent trial. Some of these methods use multivariate models for characterizing the different grades of toxicities as a function of dose while others summarize the information from all toxicity grades into a continuous score.

In particular, Van Meter et al. [17] extended the Continual Reassessment Method (CRM) with the assumption of proportional odds considering toxicities grades 0 (absence), 1, 2, 3, and 4-5. Tighiouart et al. [18] proposed the proportional odds Escalation With Overdose Control (EWOC) modeling toxicities 0-1, 2, 3-5. They both show some benefits either in safety or precision of the MTD estimate when lower grade toxicities are incorporated in comparison to the classical designs [19,20] for single agent.

Even though dose-finding designs for two agents have been the focus of statistical research in the last decade [21–33], all the proposed designs for two agents ignore lower grade toxicities. Noteworthily, Tighiouart et al. [33] presents an early phase

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I EWOC design that estimates a MTD curve lying anywhere within the Cartesian plane defined by the range of the continuous doses of two agents.

Thus we propose to extend such phase I design modeling toxicities 0-1, 2 and 3-4 with the proportional odds assumption similarly as done in [18]. This manuscript is organized as follows: section 2 poses the proportional odds model for two agents and trial design using EWOC and CRM schemes; section 3 describes the simulation scenarios and the operating characteristics for grade and binary toxicity; section 4 presents some concluding remarks.

2. Method

2.1 Dose-Toxicity Model

Let $G = 0, 1, \ldots, 4$ be the maximum grade of toxicity experienced by a patient by the end of one cycle of therapy and define DLT as a maximum of grade 3 or 4 toxicity. Let Z indicates the aggregated maximum grade of toxicity defined below

$$Z = \begin{cases} 0 & \text{if } G = 0, 1 \\ 1 & \text{if } G = 2 \\ 2 & \text{if } G = 3, 4, \end{cases} \tag{2.1}$$

such that $Z \sim \text{Multinomial}(p_1, p_2, p_3)$ where $p_i = P(Z = i)$. The cytotoxic agents are denoted by A with doses $x \in [X_{min}, X_{max}]$ and B with doses $y \in [Y_{min}, Y_{max}]$. A dose-toxicity model can be considered as

$$P(Z \geq z|x, y) = F(\alpha_z + \beta x + \gamma y + \eta xy) \quad \text{for } z = 1, 2, \tag{2.2}$$

where $F(.)$ is a known cumulative distribution function (cdf), x is the standardized dose level of agent A, y is the standardized dose level of agent B. We will assume that the probability of DLT increases with the dose of any one of the agents when the other one is held constant. A necessary and sufficient condition for this to hold is to assume that $\beta > 0, \gamma > 0$, and $\eta > 0$. In addition, $\alpha_2 < \alpha_1$ since F is strictly increasing cdf.

In this way, the MTD is defined as any dose combination (x^*, y^*) satisfying

$$P(Z = 2|x^*, y^*) = \theta, \tag{2.3}$$

where θ is a target probability pre-specified by the clinicians and depends on the severity and clinical manageability of the DLT; it is set relatively high when the DLT is a transient, correctable, or nonfatal condition and low when it is lethal or life threatening.

Then a set C of dose combinations can be characterized as MTD from (2.2) and (2.3),

$$C = \left\{ (x^*, y^*) : y^* = \frac{F^{-1}(\theta) - \alpha_2 - \beta x^*}{\gamma + \eta x^*} \right\}. \tag{2.4}$$

Model (2.2) can be reparametrized with parameters that clinicians can easily interpret. These are ρ_{200}, the probability of grade toxicity 3 or 4 (DLT) at dose $(0, 0)$, ρ_{100}, the probability of grade 2 toxicity or more at dose $(0, 0)$, ρ_{210}, the probability of grade 3 or 4 toxicity (DLT) at dose $(1, 0)$, and ρ_{201}, the probability of grade 3 or 4 toxicity (DLT) at dose $(0, 1)$. The restrictions $\beta, \gamma \geq 0$ and $\alpha_2 \leq \alpha_1$ translate into $\rho_{200} < min\{\rho_{210}, \rho_{201}\}$ and $\rho_{200} < \rho_{100}$, respectively.

The original parametrization can be recovered as follows

$$\begin{aligned} \alpha_1 &= F^{-1}(\rho_{100}) \\ \alpha_2 &= F^{-1}(\rho_{200}) \\ \beta &= F^{-1}(\rho_{210}) - F^{-1}(\rho_{200}) \\ \gamma &= F^{-1}(\rho_{201}) - F^{-1}(\rho_{200}). \end{aligned} \tag{2.5}$$

Similarly, the MTD set can be rewritten as

$$C = \left\{ (x^*, y^*) : y^* = \frac{F^{-1}(\theta) - F^{-1}(\rho_{200}) - [F^{-1}(\rho_{210}) - F^{-1}(\rho_{200})]x^*}{[F^{-1}(\rho_{201}) - F^{-1}(\rho_{200})] + \eta x^*} \right\}. \tag{2.6}$$

2.2 Prior and posterior distributions

The parameters are assumed independent a priori with $\rho_{100} \sim Beta(a_{100}, b_{100})$, $\rho_{210} \sim Beta(a_{210}, b_{210})$, $\rho_{201} \sim Beta(a_{201}, b_{201})$, and conditionally on $\rho_{210}, \rho_{201}, \rho_{100}$, $\rho_{200}/min\{\rho_{210}, \rho_{201}, \rho_{100}\} \sim Beta(a_{200}, b_{200})$. The prior distribution for the interaction parameter η is given by a $Gamma$ distribution with mean $E(\eta) = a/b$ and variance $Var(\eta) = a/b^2$.

Let $D_n = \{(x_i, y_i, z_i), i = 1, \ldots, n\}$ be the data after enrolling n patients in the trial. Using Bayes rule, the posterior distribution of the model parameters is proportional to the product of the likelihood and prior distribution

$$\begin{aligned} &\pi(\rho_{210}, \rho_{201}, \rho_{200}, \rho_{100}, \eta | D_n) \\ &\quad \propto \prod_{i=1}^{n} H_1(\rho_{210}, \rho_{201}, \rho_{200}, \rho_{100}, \eta; x_i, y_i)^{I(z_i=0)} \\ &\quad \times [H_1(\rho_{210}, \rho_{201}, \rho_{200}, \rho_{100}, \eta; x_i, y_i) - H_2(\rho_{210}, \rho_{201}, \rho_{200}, \eta; x_i, y_i)]^{I(z_i=1)} \\ &\quad \times H_2(\rho_{210}, \rho_{201}, \rho_{200}, \eta; x_i, y_i)^{I(z_i=2)} \pi(\rho_{210}, \rho_{201}, \rho_{200}, \rho_{100}, \eta), \end{aligned} \tag{2.7}$$

where

$$\begin{aligned} &H_1(\rho_{210}, \rho_{201}, \rho_{200}, \rho_{100}, \eta; x, y) \\ &\quad = 1 - F(F^{-1}(\rho_{100}) + [F^{-1}(\rho_{210}) - F^{-1}(\rho_{200})]x + [F^{-1}(\rho_{201}) - F^{-1}(\rho_{200})]y + \eta xy), \\ &H_2(\rho_{210}, \rho_{201}, \rho_{200}, \eta; x, y) \\ &\quad = 1 - F(F^{-1}(\rho_{200}) + [F^{-1}(\rho_{210}) - F^{-1}(\rho_{200})]x + [F^{-1}(\rho_{201}) - F^{-1}(\rho_{200})]y + \eta xy). \end{aligned}$$

We used JAGS [34] to sample from the posterior distribution of these parameters and estimate design operating characteristics of cancer phase I trials described below.

2.3 Trial Design

We use a dose escalation/de-escalation algorithm treating cohorts of two patients simultaneously based on the Escalation With Overdose Control (EWOC) and the Continual Reassessment Method (CRM) for drug combination principles as similarly described in [33]. The design proceeds as follows:

1. Each patient in the first cohort of 2 patients receives the same dose combination $(x_1, y_1) = (x_2, y_2) = (0, 0)$.

2. In the i-cohort of 2 patients,

(a) If i is even, then patient $2i-1$ receives dose (x_{2i-1}, y_{2i-3}) and patient $2i$ receives dose (x_{2i-2}, y_{2i}), where

$$x_{2i-1} = \pi^{-1}_{\Gamma_{A|B=y_{2i-3}}}(\alpha|D_{2i-2})$$
$$y_{2i} = \pi^{-1}_{\Gamma_{B|A=x_{2i-2}}}(\alpha|D_{2i-2})$$

for EWOC criterion.

$$x_{2i-1} = \underset{x}{\operatorname{argmin}}|H_2(\hat{\rho}_{210}, \hat{\rho}_{201}, \hat{\rho}_{200}, \hat{\eta}; x, y_{2i-3}) - \theta|$$
$$y_{2i} = \underset{y}{\operatorname{argmin}}|H_2(\hat{\rho}_{210}, \hat{\rho}_{201}, \hat{\rho}_{200}, \hat{\eta}; x_{2i-2}, y) - \theta|$$

for CRM criterion.

(b) If i is odd, then patient $2i-1$ receives dose (x_{2i-3}, y_{2i-1}) and patient $2i$ receives dose (x_{2i}, y_{2i-2}), where

$$x_{2i} = \pi^{-1}_{\Gamma_{A|B=y_{2i-2}}}(\alpha|D_{2i-2})$$
$$y_{2i-1} = \pi^{-1}_{\Gamma_{B|A=x_{2i-3}}}(\alpha|D_{2i-2})$$

for EWOC criterion.

$$x_{2i} = \underset{x}{\operatorname{argmin}}|H_2(\hat{\rho}_{210}, \hat{\rho}_{201}, \hat{\rho}_{200}, \hat{\eta}; x, y_{2i}) - \theta|$$
$$y_{2i-1} = \underset{y}{\operatorname{argmin}}|H_2(\hat{\rho}_{210}, \hat{\rho}_{201}, \hat{\rho}_{200}, \hat{\eta}; x_{2i-1}, y) - \theta|$$

for CRM criterion.

3. Repeat step 2 until n patients are enrolled to the trial subject to the stopping rule.

Stopping rule: We stop enrollment to the trial if $\mathrm{P}(P(\mathrm{DLT}|(x,y) = (0,0)) > \theta + \delta_1|\mathrm{data}) > \delta_2$, i.e. if the posterior probability that the probability of DLT at the minimum available dose combination in the trial exceeds the target probability of DLT is high. The parameters δ_1 and δ_2 are design parameters chosen to achieve desirable model operating characteristics.

At the end of the trial, we estimate the MTD curve using Bayes estimates of the parameters defining this curve as

$$\hat{C} = \left\{(x^*, y^*) : y^* = \frac{F^{-1}(\theta) - F^{-1}(\hat{\rho}_{200}) - [F^{-1}(\hat{\rho}_{210}) - F^{-1}(\hat{\rho}_{200})]x^*}{[F^{-1}(\hat{\rho}_{201}) - F^{-1}(\hat{\rho}_{200})] + \hat{\eta}x^*}\right\}, \quad (2.8)$$

where $\hat{\rho}_{200}, \hat{\rho}_{100}, \hat{\rho}_{210}, \hat{\rho}_{201}, \hat{\eta}$ are the posterior medians given the data D_n.

3. Simulations

3.1 Set-up and scenarios

We studied four scenarios for the true continuous MTD curve. In all cases, the target probability of DLT is fixed at $\theta = 0.33$ and the trial sample size is $n = 42$ patients. Scenario (1), $(\rho_{100}, \rho_{200}, \rho_{210}, \rho_{201}, \eta) = (2\times10^{-7}, 10^{-7}, 3\times10^{-6}, 3\times10^{-6}, 10)$, shows two drugs that are very safe within the range of available doses in the trial but the

true MTD curve lies near the upper-right corner of the xy plane. In scenario (2), $(0.005, 0.001, 0.01, 0.6, 10)$, the MTD of agent A when agent B is at its minimum dose level is within the range of doses of drug A but the MTD of agent B when drug A is at its minimum dose level is above the maximum dose level of agent B. Scenario (3), $(0.05, 0.01, 0.9, 0.2, 100)$, is a case where drug A is safe but the MTD of agent B when drug A is at its minimum dose level is just above 0.8 and scenario (4) (0.25, 0.2, 0.9, 0.9, 100) presents a very low MTD curve with high probability of grade 2 toxicity.

3.2 Operating Characteristics

We evaluate the performance of the two designs using CRM and EWOC schemes by assessing the safety of the trial designs as well as the efficiency of the estimate of the MTD curve based on 1000 simulated trials.

3.2.1 Safety

We assess trial safety by reporting the average percent of grade 3 DLT across all 1000 trials and the percent of trials that have a DLT rate exceeding $\theta+\delta$, for $\delta = 0.1$. The threshold $\theta + 0.1$ is usually considered to be an indication of an excessive DLT rate.

3.2.2 Efficiency

We present an estimate of the MTD curve using the average posterior medians of the model parameters. Under the reparameterization, the estimate is

$$\hat{C} = \left\{ (x^*, y^*) : y^* = \frac{(F^{-1}(\theta) - F^{-1}(\hat{\rho}_{200})) - (F^{-1}(\hat{\rho}_{210}) - F^{-1}(\hat{\rho}_{200}))x^*}{(F^{-1}(\hat{\rho}_{201}) - F^{-1}(\hat{\rho}_{200})) + \hat{\eta}x^*} \right\}, \quad (3.1)$$

where $F(.)$ is the logistic function and $\hat{\rho}_{200}, \hat{\rho}_{201}, \hat{\rho}_{210}, \hat{\eta}$ are the average posterior medians of the parameters $\rho_{200}, \rho_{201}, \rho_{210}, \eta$ from all $m = 1000$ trials. The next measure of efficiency is the pointwise average relative minimum distance from the true MTD curve to the estimated MTD curve. For $i = 1, \ldots, m$, let C_i be the estimated MTD curve and C_{true} be the true MTD curve. For every point $(x, y) \in C_{true}$, let

$$d^{(i)}_{(x,y)} = sign(y' - y) \times min_{\{(x^*,y^*):(x^*,y^*)\in C_i\}}((x - x^*)^2 + (y - y^*)^2)^{1/2}, \quad (3.2)$$

where y' is such that $(x, y') \in C_i$. This is the minimum relative distance of the point (x, y) on the true MTD curve to the estimated MTD curve C_i. If the point (x, y) is below C_i, then $d^{(i)}_{(x,y)}$ is positive. Otherwise, it is negative. Let

$$d_{(x,y)} = \frac{1}{m} \sum_{i=1}^{m} d^{(i)}_{(x,y)}. \quad (3.3)$$

This is the pointwise average relative minimum distance from the true MTD curve to the estimated MTD curve and can be interpreted as the pointwise average bias in estimating the MTD. Let $\Delta(x, y)$ be the Euclidian distance between the minimum dose combination $(0, 0)$ and the point (x, y) on the true MTD curve and $0 < p < 1$. The last measure of efficiency we consider is

$$P_{(x,y)} = \frac{1}{m} \sum_{i=1}^{m} I(|d^{(i)}_{(x,y)}| \leq p\Delta(x, y)). \quad (3.4)$$

This is the pointwise percent of trials for which the minimum distance of the point (x, y) on the true MTD curve to the estimated MTD curve C_i is no more than $(100 \times p)\%$ of the true MTD. This statistic is equivalent to drawing a circle with center (x, y) on the true MTD curve and radius $p\Delta(x, y)$ and calculating the percent of trials with MTD curve estimate C_i falling inside the circle. This will give us the percent of trials with MTD recommendation within $(100 \times p)\%$ of the true MTD for a given tolerance p.

3.3 Results

Table 1 presents the average percent of DLTs varies between 8.28% and 43.53% for the design with a binary indicator of DLT and 16.54% and 44.12% for the design with ordinal toxicity grades. In addition, the percent of trials with an excessive DLT rate is less than 1% for the first two scenarios. The last scenario still needs further investigation since the results are the opposite as expected.

Figure 1 shows the plots of the true and estimated MTD curves obtained using (3.1). The two designs are similar for both schemes EWOC and CRM in the four scenarios.

Figure 2 displays the pointwise average relative minimum distance from the true MTD curve to the estimated MTD curved under the four scenarios (1)-(4) as defined in (3.3). Under scenarios (1) and (4), the proposed design with ordinal grades has relatively smaller pointwise average bias, and the difference between two designs is negligible for scenarios (2) and (3).

Figure 3 contains the pointwise percent of MTD recommendation for tolerance p = 0.2 as defined in (3.4). Under scenario (1), the proposed design with ordinal toxicity grades is better than the design with a binary indicator of DLT; under scenarios (2) and (3), there is no difference between designs, and in scenario (4) the binary designs present higher percent values than the ordinal designs for EWOC and the difference is ignorable for CRM.

Table 1: Average DLT rate and % trials: DLT rate $> \theta + 0.10$ under scenarios (1)-(4)

Scenario	Design	Average % DLTs G3		%Trials: DLT rate G3 > 0.43	
		Binary	Ordinal	Binary	Ordinal
1	EWOC	8.28	16.54	0.0	0.0
	CRM	9.28	19.35	0.0	0.0
2	EWOC	25.28	23.55	0.0	0.0
	CRM	27.77	25.93	0.0	0.0
3	EWOC	32.82	33.26	0.1	0.3
	CRM	34.00	33.81	0.1	0.5
4	EWOC	43.53	44.12	44.2	48.6
	CRM	39.50	41.43	11.5	27.0

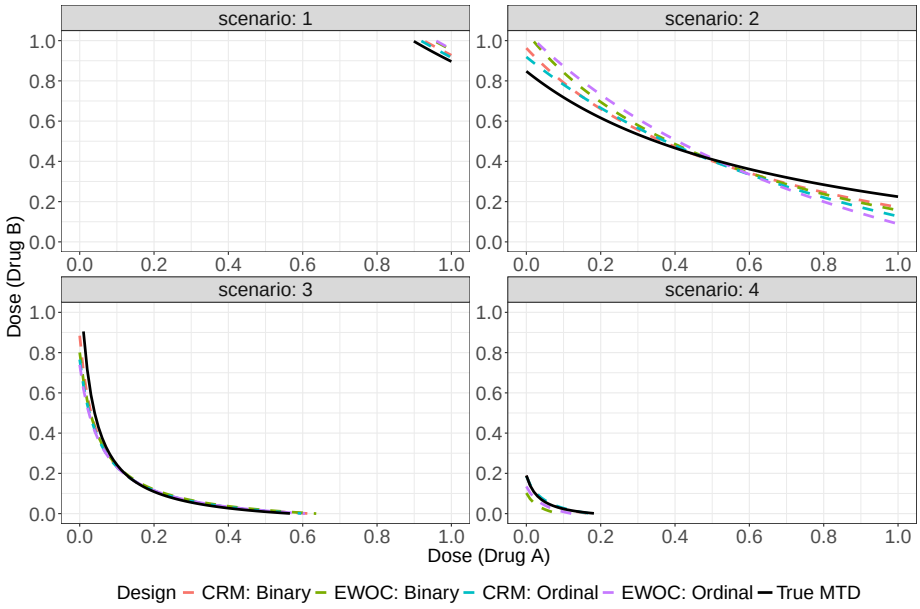

Figure 1: True and estimated MTD curves under scenarios (1)-(4)

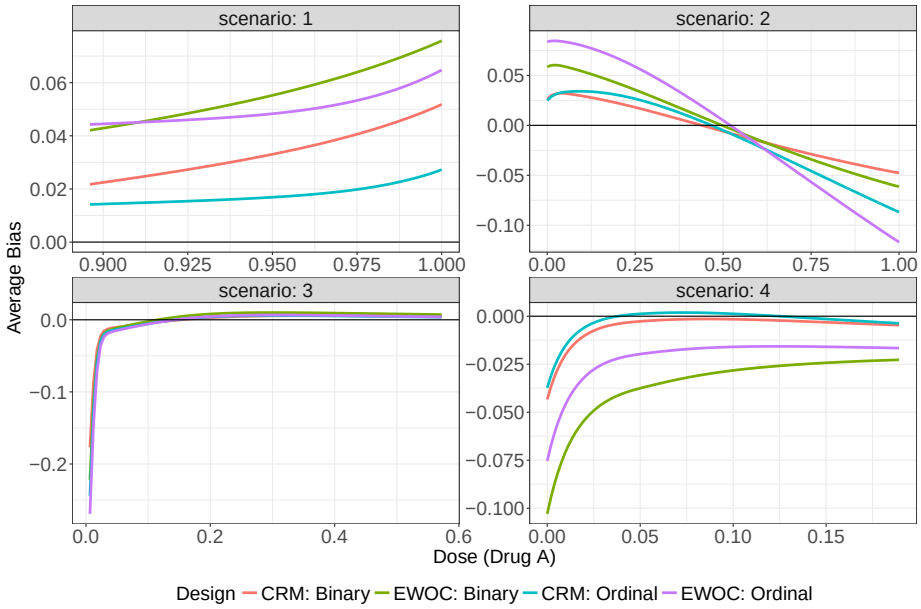

Figure 2: Pointwise average relative minimum distance from the true MTD curve to the estimated MTD curve under scenarios (1)-(4)

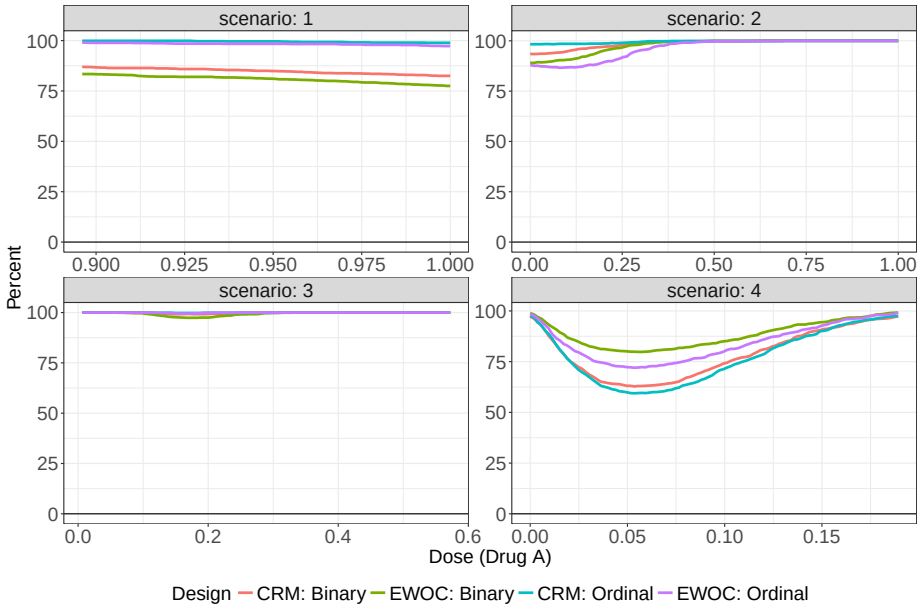

Figure 3: Pointwise percent of MTD recommendation for p = 0.2 under scenarios (1)-(4)

4. Concluding Remarks

We described Bayesian adaptive designs for cancer phase I clinical trials using two drugs with continuous dose levels taking into account lower grade toxicities. We compared these results to Tighiouart et al. [33]. In each case, vague priors were used for quantifying the toxicity profile of each agent a priori. We studied design operating characteristics of the methodology under four practical scenarios. The binary and ordinal designs are similar in efficiency and safety even though more information is being used in the ordinal design. Further investigation under different scenarios is still needed.

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