**Dose Escalation with Over-dose and Under-dose Control**

**Using a quasi-continuous toxicity score in Phase I/II Clinical Trials**

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**Abstract**

Escalation with overdose control (EWOC) is a Bayesian adaptive design for selecting dose levels in cancer phase I clinical trials and has been carried out for many years. However, the toxicity response was treated as binary indicator of dose limiting toxicity (DLT) and underdose control was not considered in this design. Chen et al. (2010) proposed a novel toxicity scoring system to fully utilize patients’ toxicity information using a normalized equivalent toxicity score. Chen et al. (2015) extended EWOC to Phase I/II clinical trials by controlling for under-dosing (EWOUC) to provide at least minimum efficacy of drug. In this paper, we developed EWOUC-NETS based on these two methods to combine their advantages. Additionally, we further extended this study by treating efficacy outcome as also continuous and recommended dose (RD) was chosen based primarily on Bayesian method. The dose escalation decision rules were based on the posterior distribution of both toxicity and efficacy outcomes. We compared the operation characteristics of the proposed and existing methods through simulation studies under five scenarios. We found that EWOUC-NETS with continuous efficacy outcome effectively increased the efficacy reduced the probability of excess doses in almost all scenarios.

1. **Introduction**

One of the most important steps in drug development is Phase I cancer clinical trials. Phase I trials are conducted to evaluate a new drug’s toxic effect on patients and to find the optimal dose, called the maximum tolerated dose (MTD). MTD is defined as the dose at which the probability of dose limiting toxicity (DLT) is equal or close to the target toxicity level (TTL, i.e., 33%). The main objective of a cancer Phase I clinical trial is to MTD estimation under safe administration and acceptable level of adverse events using toxicity responses. Among a variety of existing Phase I clinical trial designs, escalation with overdose control (EWOC), proposed by [1], is one of the most popular Bayesian dose-finding method. Numerous extensions of the EWOC have been proposed to improve the performance and to adapt for more complicated dose-finding problems. For instance, [2] have developed a method utilizing varying feasibility bound in the EWOUC design. In addition, [3] proposed a novel normalized equivalent toxicity score (NETS) system to fully utilize the toxicity information of patients and integrated NETS with EWOC, called EWOC-NETS, which can increase the accuracy of the EWOC estimation. [4] proposed another extended version of EWOC – dose escalation with overdose and underdose control (EWOUC) in Phase I/II clinical trials. This method provides patients with at least minimum drug efficacy.

In the EWOUC design, binary indicators of dose limiting toxicity (DLT) (whether DLT occurs during the observation window of one cycle of therapy) and efficacy event (whether a patient experiences an efficacy event during the observation window of one cycle of therapy) are used to describe the toxicity and efficacy outcomes. However, after incorporating efficacy into a dose-finding design, researchers might further utilize the efficacy data to reduce the loss of information. In some studies, the efficacy endpoint to evaluate antitumor activity is considered to be binary (e.g., response or non-response) on the basis of a threshold for tumor shrinkage as a continuous variable. However, categorization of continuous variables usually results in a considerable loss of information, which to some extent reduces the statistical efficiency. To address this issue, a new dose-finding approach for correlated continuous toxicity and efficacy outcomes in Phase I/II oncology trials is required.

[5] proposed an adaptive dose-finding approach for treating correlated bivariate binary toxicity and continuous efficacy outcomes. Incorporating this method and NETS, we propose a new Bayesian dose-finding method in the framework of EWOC-NETS and EWOUC, called EWOUC-NETS, using correlated bivariate continuous toxicity and efficacy outcomes. Our design treats toxicity and efficacy as dual endpoints.

Although toxicity outcomes can be observed in time, efficacy outcomes usually take longer time to estimated. This means that the efficacy outcomes cannot be observed quickly enough to apply the adaptive decision rule to determine the recommended dose for new patients. In order to solve the problem of delay in efficacy estimation, we extended our methodology using data augmentation (DA), proposed by [6]. We refer to the new design as the EWOUC-NETS-DA. It contains EWOUC-NETS as a special case with efficacy outcomes immediately observable. We only consider efficacy outcomes to be delayed because in most cases toxicity of cytotoxic agents is acute. Nevertheless, this data-augmentation method can be also applied on delayed toxicity as well [6].

Our methodology is established based on the EWOUC framework. The EWOUC design provides over-dose and under-dose control to protect patients from severe toxicity and ensure minimal efficacy at the same time. However, it does not incorporate NETS and still treats efficacy as binary indicator. This motivated us to develop new designs with aims: (1) Use NETS to estimate toxicity outcome; (2) Use continuous efficacy outcome; (3) accommodate delayed efficacy to support continual patient enrollment.

The remainder of the manuscript is organized as follows. In Section 2, we introduce the probability models, dose finding algorithm and DA method to deal with delayed efficacy outcome. In Section 3, extensive simulations are presented to evaluate the performance of the EWOUC-NETS and the EWOUC-NETS-DA. In Section 4, we summarized the operating characteristics of our new design.

1. **Methods**
   1. ***Introduction of NETS***

Phase I clinical trials usually have relatively small sample sizes and therefore limited information of toxicity and efficacy. Full utilization of all toxicity data is important to improve trial efficiency and accuracy of MTD estimation. Typically, patients in the trials can experience different types and grades of toxicities varying from 0 for no toxicity to 5 for death but such information is disregarded when the toxicity is treated as a binary indicator in EWOC, which lost a lot of information. So, here we use a normalized equivalent toxicity score (NETS), to replace the binary indicator and make full use of the information to get more accurate result.

The NETS is defined as below:

(1)

where denotes the jth toxicity level of the ith patient, . represents the weight for the correlation of the jth toxicity with other toxicities for the *i*th patient. is a slope parameter and values between 0.1 and 0.5. It represents the increasing “speed” of NETS due to additional toxicity besides the worst toxicity of the patient. Obviously, we can find that depends a lot on , the maximum toxicity level of patient *i*. has been normalized with range 0 to 1 since the maximum possible value. See Table 1 for specific numerical correspondence.

A logistic function can be employed to model the relationship between dose level and the expectation of NETS for the th patient, denoted by , as:

(2)

can be considered as the average NETS (ANETS) at dose level . is a specified distribution function.

* 1. ***Outcome model and re-parameterization***

Let and denote the outcomes of NETS and a continuous efficacy variable. They are both assumed to be truncated normal distributed with range 0 to 1. So, the raw continuous efficacy outcome needs to be transformed by before formulating the model. [7] proposed a novel adaptive dose-finding approach to handle correlated continuous efficacy outcome and binary toxicity outcome. The distribution of efficacy outcome in our method is established based on their framework, but fewer parameters need to be estimated.

We assume the marginal distribution of and follow the distributions below:

(3)

(4)

Where is assumed to have a logistic relationship with dose levels:

(5)

It is also assumed that:

(6)

Where and are unknown parameters. This is the multiplicative heteroscedasticity proposed by Harvey [8]. The parameter controls the degree of heteroscedasticity. The homoscedasticity is held when .

The correlation between toxicity and efficacy outcomes should also be taken into consideration. We still use NETS, denoted as , as the toxicity outcome. The model we are using is based on the factorization of the joint distribution of ():

(7)

Given , we assume that the distribution of is normal:

(8)

Where is the parameter for the regression of on S. Large absolute values of indicate a strong correlation between the two outcomes. When = 0, the two outcomes are independent given the dose level of the agent in the model. The correlation based on this model is

(9)

However, in the above dose-toxicity and dose-efficacy relationships do not have clear clinical meanings. In order to provide clinical interpretation for dose-toxicity relationship, re-parameterization is needed, using parameters that are easy to be interpreted in a clinical way: MTD (), NETS () at the starting dose , target normalized equivalent toxicity score () as below:

(10)

(11)

Then, the two original parameters and can be re-written as follows:

(12)

(13)

Hence, if plugging in (12) and (13) into (2), we can re-write the dose-toxicity relationship as:

(14)

Similarly, the dose-efficacy relationship can also be re-parameterized, using MED (), efficacy outcome () at the starting dose and expected efficacy at MED ():

(15)

(16)

Correspondingly, and can be re-written as follows using (10) and (11):

(17)

(18)

Therefore, the dose-efficacy relationship (5) can be interpreted using parameters that have clear clinical meanings with (17) and (18):

(19)

Suppose that patients have been treated in the clinical trial, resulting in the NETS and continuous efficacy data . The likelihood function is given by (20) as:

(20)

Where . Let denote the prior distribution of , then the posterior distribution of is given by (21) as:

(21)

In order to define , and are assigned to have uniform distributions in the interval and , where is a small positive value. Meanwhile, and are assigned to be non-informative uniform prior distributed in the interval , where is the maximum dose under investigation or determined by pre-clinical studies. When <, the trial will be terminated early because of high toxicity. When >, the trial will be terminated early without a dose level being recommended, or new higher dose levels need to be added because no pre-specified dose levels meet the minimum efficacy requirement. When > and <, the trial will choose the dose with the highest utility.

* 1. ***Over-dose and under-dose control***

As [4] proposed for the EWOUC method, in order to offer patients maximum benefit, we should prevent letting patients be exposed to overly toxic doses (i.e., doses above , the MTD) or low doses that cannot provide therapeutical effects (i.e., doses below , the MED). Hence, it is ideal that patients are treated at doses between and . Therefore, the trial should be terminated if is greater than and we cannot select any doses for further study as there is no doses that are both safe and efficacious. However, if there is an interval between the MED and MTD (i.e., ), investigational doses could be chosen within this interval to treat patients to ensure safety and minimum efficacy.

Suppose that patients have been treated in the clinical trial. The investigational dose for the incoming patient should satisfy both over-dose condition (22),

(22)

and the under-dose control condition (23),

(23)

where and are the feasibility bounds for toxicity and efficacy, respectively. These two conditions ensure that the probability of overly toxic dosing is less than , and the probability of under dosing is , given the currently observed clinical data. Additionally, the values of and usually vary as the trial proceeds, because information is limited at the beginning of the trial. Thus, using smaller value of and larger value of initially is preferred to estimate the MTD and the MED. As more data about the MED and MTD are collected during the trial, less conservative over-dose and under-dose controls can be utilized.  is set at 0.25 and its value is increased by a step size of 0.05 after each enrollment of new cohorts until the value of reaches 0.5. [4] showed that using their varying feasibility bound, , improves the speed of posterior estimation of the MTD to converge to the true MTD. Accordingly, is set to be decreased from 0.75 by a step size of 0.05 until it reaches 0.5. This under-dose control method has also been proved to be efficient in [4].

In most cases, more than one investigational dose satisfies the over-dose and under-dose control conditions. These doses are called an acceptable dose set. To select one dose from the acceptable dose set for the incoming patient, the utility function is defined to evaluate each dose in the acceptable dose set:

,

where is the penalty term induced by toxicity. evaluates the tradeoff between the mean toxicity and the mean efficacy at a certain dose . Larger values of imply heavy penalty on toxicity, resulting in doses with low toxicity. The recommended dose chosen from the acceptable dose set would be the one with the highest utility (i.e., the highest value of ).

The dose-finding algorithm for our proposed design can be summarized as follows:

1. Treat the first cohort of patients at the minimum dose, .
2. Given the current cumulative clinical data , update the posterior distribution , and decide the recommended dose for the next cohort of patients that satisfies both over-dose and under-dose control conditions (22) and (23), with the highest posterior mean of utility, . However, if there are no doses fall within the acceptable dose set, the trial should be terminated.
3. Repeat steps 1) to 2), until the trial reaches the maximum sample size. Select the dose with the highest posterior mean to treat the next cohort of patients. This dose is the final recommended dose, called the optimized utility dose (OUD).
   1. ***Delayed efficacy***

In many cases, efficacy outcome is not immediately observable while the toxicity outcome can be quickly ascertainable, resulting in so-called delayed efficacy. Hence, at the moment of deciding the dose assignment, efficacy outcomes of some patients still remain unobserved. These efficacy outcomes are therefore considered missing. However, these missing efficacy outcomes cannot be ignored according to [9]. Hence, we use a Bayesian data augmentation method proposed in [4] to handle delayed efficacy.

Let denote a follow-up time window for efficacy evaluation. If the th patient does not experience any efficacy event within , . Let denote the time to efficacy and let denote the actual time that clinical researchers need to make the decision of dose assignment for the next patient. When and (i.e., the patient has not completed the follow-up time and the actual time to make decision is shorter than the time to efficacy), is missing. Let be a missing indicator with when is missing. [4] proposed a specified piecewise exponential model for . We partition the follow-up time window into K intervals where . It is also assumed that each interval has a constant hazard rate . The value of K affects the smoothness of the model. For example, the fitted curve would be smoother when K is larger. The value of K is decided using Deviance Information Criterion. Let as the observed time-to-event. For patients, we have . Then the likelihood function of can be written as:

(24)

where and 0 otherwise. is defined as 1 if the *ith* patient experienced an efficacy event in [*hk-1, hk*) or 0 otherwise. Since the posterior ofis unimodal distributed, can be identified by its posterior median.

1. **Simulation**

***3.1 Simulation settings***

EWOUC-NETS is simulated with three different versions: EWOUC-NETS-Comp (EWOUC-NETS with complete data, which waits and fully observes the patients’ efficacy outcome before the enrollment of the next new patient), EWOUC-NETS-NW (EWOUC-NETS with incomplete data, not waiting for the efficacy outcome to be observed, which considers unobserved efficacy outcome as non-response and enrolls patients in real time), and EWOUC-NETS-DA (EWOUC-NETS using DA to handle missing efficacy data, which algorithm is described in [4]). These three versions of EWOUC-NETS are compared with EWOC, EWOUC-Comp, EWOUC-NW and EWOUC-DA. Here the EWOC also waits for efficacy outcome to be fully observed and uses complete data to estimate the MTD. The comparisons between EWOUC-NETS-Comp, EWOUC-NETS-NW and EWOUC-NETS-DA evaluates the efficiency of EWOUC-NETS-NW and EWOUC-NETS-DA on dealing with delayed efficacy outcome. The comparison between EWOUC-NETS methods and EWOC, EWOUC methods provides assessments on efficiency of additional under-dose control and the utilization of NETS and continuous efficacy outcome.

Three main aspects are compared between the designs: the accuracy of dose recommendation, therapeutic effects, and trial duration, under five different scenarios (Table 1). These scenarios simulate the different situations that could be encountered in a solid tumor trial. Scenario 1 (S1) is corresponded with an extremely good agent. Scenario 2 (S2), Scenario 3 (S3), Scenario 4 (S4) and Scenario 5 (S5) correspond to a good agent, a moderate agent, a bad agent and an extremely bad agent, respectively. Five dose levels (0.2, 0.4, 0.6, 0.8, and 1.0) are studied. Based on [3], the targeted normalized equivalent score would be 0.476, and it is also set to be the highest tolerated toxicity rate . Also, the minimal efficacy bound , is 0.3. The MTDs and MEDs under each scenario are summarized in Figure 1. is set for all scenarios. It is assumed in the simulation settings that the toxicity outcome can be observed immediately, but it takes three months to assess the efficacy outcome of patients. The number of patients used for each trial is set to be 30 unless the trial is terminated in advance. The Metropolis-Hastings algorithm is used to sample from posterior distribution. The first 1000 iterations are treated as burn-in period and only the last 1000 iterations are utilized as the sample from posterior distribution. 1000 simulations are repeated for each scenario.

* 1. ***Dose identification accuracy***

The accuracy of final dose recommended for the next patient is one of the most important factors to evaluate the performance of trial designs. We compare EWOUC-NETS-Comp with EWOC and EWOUC-comp to evaluate the additional effect of using continuous toxicity and efficacy outcomes. EWOUC-NETS-Comp utilized the best utility to identify the recommended dose level for S1, S2 and S3. The OUD identified in these three scenarios are dose level 4, dose level 3 and dose level 4, respectively. For Scenario 1, EWOUC-NETS-Comp has a different recommended dose level than EWOC and EWOUC-NETS. However, it is reasonable, as it reaches the highest value of utility and satisfies the over-dose and under-dose control. EWOUC-NETS-Comp has the same recommended dose levels with EWOUC-Comp and EWOC in S2 and S3. The dose identified percentages for the OUD by the EWOUC-NETS-Comp are 72.7%, 56.8% and 83.0% for S1, S2 and S3, respectively. Since no targeted dose found in S4 and S5, the trial should be terminated early under S4 and S5. EWOC chooses a dose level by using the true MTD rather than the OUD. However, this could be more toxic in the future clinical studies. The dose level selected by EWOUC-Comp and EWOUC-NETS-Comp are less toxic since they take into account the minimum efficacy and the highest utility. EWOUC-NETS-Comp provides a more reasonable result than EWOUC-Comp as the dose level remains within the acceptable dose set but with higher dosage, which is usually more efficacious.

Then we want to evaluate the performance of the DA algorithm in handling delayed efficacy. Hence, the EWOUC-NETS-DA is compared with EWOUC-NETS-NW and EWOUC-NETS-Comp under each scenario. The EWOUC-NETS-DA has higher dose recommendation percentage at the OUD than EWOUC-NETS-NW under S1, S2 and S3. More patients are treated at the OUD using EWOUC-NETS-DA than using EWOUC-NETS-NW (51.57% vs 61.28% in S1, 42.90% vs 48.78% in S2, and 57.18% vs 62.03% in S3). Less percentage of patients are treated above the OUD by EWOUC-NETS-DA, which ensures higher safety. Nevertheless, these three versions of EWOUC-NETS all stop the trial early under S4 and S5, because no targeted dose level is found within the acceptable dose set. In the case of bad (S4) and extremely bad (S5) agents, the average sample sizes are 15.851 for EWOUC-NETS-NW, and 19.085 for EWOUC-NETS-DA. EWOUC-NETS-NW has smaller sample size because it simply ignores incomplete data and overestimate MED.

* 1. ***Sensitivity analysis***

We want to examine the robustness of the EWOUC-NETS design under relatively good scenarios (S1, S2 and S3) using more combinations of () in extensive simulations, where is set to be 1, 2 and 3 in the joint model and is set to be 0.3 and 0.4.

* 1. ***Application using a real trial example***

1. ***Conclusion and discussion***

In this paper, we extend the EWOUC design by incorporating NETS and continuous efficacy. The over-dose control and under-dose control ensures safety and improves the therapeutic effect for patients. In addition, the application DA algorithm in the EWOUC-NETS-DA design is used to handle delayed efficacy. The DA algorithm also improves the trial efficiency and increases the accuracy of final dose estimation for subsequent clinical trials.

In the EWOUC-NETS design, NETS [4] is employed to model the toxicity outcome while the efficacy is also considered to be continuous by using the factorization model proposed in [5]. In this paper, we proposed a novel model to model the joint probability of toxicity events and efficacy outcomes. Using EWOUC-NETS, we can fully utilize the toxicity and efficacy information of patients in trials and provide more accurate final dose estimation with higher safety and better therapeutic effects. Through extensive simulation studies, we have found that EWOUC-NETS functions well in identifying a recommended dose between the MED and the MTD with the best utility. Under S1 and S3, the average NETS of EWOUC-NETS designs are smaller than the DLT rates of EWOC and EWOUC designs. Under S2, the average NETS are slightly larger or similar to the average rates of EWOC and EWOUC designs. It might not be suitable to directly compare the average NETS and the average DLT rates, as the DLT rates cannot fully present and utilize the toxicity information of patients. Therefore, the DLT rates are not accurate to represent the toxicity outcomes.

The future research can involve the joint determination of multiple drug doses and personalized dose determination due to people’s different tolerance to the drugs, which is more accurate. So, this work can also be conducted in statistical genetics. Moreover, we can also extend the current EWOUC-NETS design from one single drug to two or multiple drugs, since most of the time, patients take more than one drug in a period, and there may exist drug interactions.

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**REFERENCES:**