**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 with similar DLT rate.

**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.