A DOSE-FINDING APPROACH BASED ON SHRUNKEN PREDICTIVE PROBABILITY
FOR COMBINATIONS OF TWO AGENTS IN PHASE I TRIALS

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Dose-finding trials for combinations of two agents have rapidly increased in oncology; simultaneously, many Bayesian dose-finding designs for such trials have been developed. When adopting these designs without prior information about the tested agents, an independent, vague, prior distribution is often assumed for each parameter to achieve the likelihood that dominates the posterior estimation. The choice of prior distributions including the specification of the values of hyperparameters is arbitrary, which can have a significant effect on the operating characteristics of the selected dose-finding design. To accommodate dose-finding using only the likelihood for the combination of two agents, we develop a novel likelihood-based, dose-finding approach based on the predictive probability of toxicity estimated in a shrinkage manner. In this proposed method, the toxicity outcome is constructed by a new shrinkage logistic regression model that assumes different shrinkage multipliers for each coefficient. We based the dose-escalation/de-escalation decision rules on the shrunken predictive probability of toxicity. We then compared the operating characteristics between the proposed and an existing Bayesian method through simulation studies under various scenarios. Our findings show that the proposed method could improve the recommendation rates for the true recommended dose combinations and further decrease the recommendation rates for the unacceptable toxicity dose combinations in many cases.