Bayesian designs for first-in-human phase I trials in oncology

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Abstract

First-in-human dose-escalation trials aim at determining the maximum tolerated dose (MTD) of a new treatment and its recommended phase II dose. In oncology, the tested compound is often toxic since it is expected that efficacy is linked to toxicity. As a result, phase I trials are conducted on diseased patients, resulting on challenging trials. Indeed, trials must keep the patients safe, while minimizing the number of patients treated at sub-therapeutic dose and finding the MTD quickly.

Different approaches exist to design these trials: rule-based, model-based and model-assisted designs. Since several years, regulatory agencies advocate the use of the latter two, since there are more flexible and enable for a better accuracy of the MTD. However, rule-based designs remain the most used methods in practice. This is because there are much easier to understand.

In this work, we highlights the limits of rule-based designs. Then, one model-assisted: the Bayesian Optimal Interval (BOIN) design and two-model based designs: the Continual Reassessment Method (CRM) and the Bayesian Logistic Regression Method (BLRM) are detailed. We study their operating characteristics: accuracy, and distribution of patients among doses. Finally, a comparison of these designs based on simulations is conducted. It demonstrates the superiority of the BOIN and the BLRM designs to provide an accurate MTD while balancing patients' safety and therapeutic opportunity.

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Glossary

MTD: Maximum Tolerated Dose

DLT: Dose Limiting Toxicity

BOIN: Bayesian Optimal Interval

CRM: Continual Reassessment Method

BLRM: Bayesian Logistic Regression Method

EWOC: Escalation With Overdose Control