Letter to the Editor

Clinical Cancer Research

Accuracy, Safety, and Reliability of Novel Phase I Designs—Letter

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A recently published review (1) of the accuracy, safety, and reliability of novel phase I methods concluded that the Bayesian Optimal Interval (BOIN; ref. 2) method does not suffer from the issue of "irrational" dose assignment. This property is defined by the authors as failing to deescalate the dose when 2 of 3 or $\geq$3 of 6 patients had dose-limiting toxicities (DLT) at a dose. This letter examines the author's definition of irrational dose assignment in a simulated trial example using the BOIN method. We generated DLT outcomes under an assumed set of true DLT probabilities (0.18, 0.25, 0.32, 0.36, 0.60, 0.69; Scenario 2 in Supplementary Table S2 of Zhou and colleagues; ref. 1) for a trial of $n = 36$ patients in cohorts of size 1. The target DLT rate is 25%, which yields dose escalation and deescalation boundaries of 19.7% and 29.8%, respectively. The allocation decisions of the BOIN method for the simulated trial are reported in Fig. 1. Note that patient 15 is the third of 6 patients to have a DLT with dose 3. Thus, the dose assignment for patient 16 is deescalated to dose 2, a decision that is classified as "rational" by the authors (1). However, the BOIN method recommends returning to dose level 3 with patient 17 immediately after a DLT is observed at dose level 2 in patient 16. In fact, no matter what DLT outcome was observed for patient 16, the observed DLT rate at dose level 2, either 0 of 6 or 1 of 6, would guarantee that the BOIN method would return to dose level 3 for patient 17. Therefore, the information obtained from the participation of patient 16 in the study does not contribute to the dose assignment algorithm for patient 17. Overall, data observed for 8 of 36 (22%) patients accrued to the study (patients 9, 13, 16, 17, 19, 21, 23, and 30) do not inform the dosing decision for the following patient accrued to the study. It is not clinically sensible to view as irrational the failing to deescalate when $\geq$3 of 6 patients experienced DLTs, but then allow, as rational, returning to that dose when the very next patient has a DLT at the next lowest dose level. While this simulated trial constitutes only a single example of a behavior of the BOIN method that would not be clinically acceptable, we hope that it will encourage researchers to take a closer look at in-trial behavior of new phase I methods.

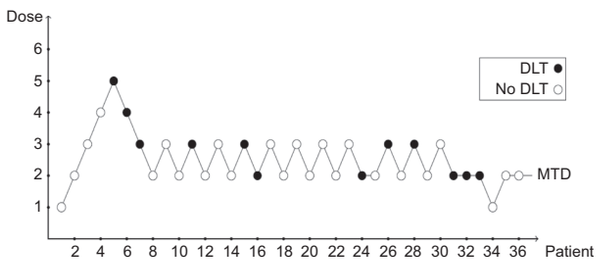

Figure 1.
Simulated trial example of the Bayesian optimal interval design for $n = 36$ patients under Scenario 2 in Supplementary Table S2 of Zhou and colleagues (1) The design escalates if the observed DLT rate at the current dose level $\leq$19.7%. The design deescalates if the observed DLT rate at the current dose level is $\geq$29.8%. Otherwise, the current dose level is retained.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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