OPERATION STRATEGY OF PHASE I TRIALS IN CANCER.

Naoki Ishizuka[1], Takashi Taniguchi[2]

[1] Department of Community Health and Medicine, Research Institute, International Medical Center of Japan, Japan
[2] Post Marketing Development, Pharmaceutical Development Department, Yakult Honsha Co.,Ltd., Japan

Phase I trials in cancer is solely adaptive. The Continual Reassessment Method (CRM) enables to update an assumed dose-response model with each patient's response in Bayesian fashion while conventional design requires three patients to decide to escalate dose or add another three patients, otherwise terminate the trial. A modified version of CRM with two or three patients' cohort has also been proposed. Papers in medical journals show many applications of the modified CRM. The TIme To Event CRM (TITE-CRM) is also proposed and has been applied to some trials which are interested in late onset toxicity. Compared with ordinal CRM and conventional design, the advantage of rapid accrual of patients was empathized. However, drop-out due to low efficacy or non dose limiting toxicity (DLT) in the study is inevitable and censoring mechanism for the above reason is dose-dependent in TITE-CRM while most of cyto-toxic drugs are evaluated with in one or two cycle to evaluate toxicity.

Some clinicians think investigators must wait for each patient's response concerning patient accrual. Those who believe so think the CRM is inferior to the conventional design in terms of patients' accrual speed. They are afraid they could not catch eligible patients while one patient is being treated in the trial.

In Bayesian sense any patients should be treated at the most promising dose level based on the all of the cumulative information including the ongoing trial. So we think at most three patients can be observed simultaneously as conventional design does. When one of these patients completes a defined cycle for treatment, the next dose level can be determined by CRM. This operation strategy with CRM design can be expected more rapid patients accrual than conventional design because it does not wait for other patient’s response in a cohort.

We evaluated the advantage of this operation strategy compared with conventional design quantitatively. The simulation study is typical one of Queuing theory in Operational Research. The simulation for our proposed operational strategy can be described as M/D/n in Kendall's fashion which means Poisson arrival for patients, a fixed service time and number of beds, with that no patient will wait until bed is open.

Our simulation result suggests that the proposed operation strategy is superior in terms of time to accomplish the target sample size, availability of beds, percentages of patients who enrolled in all of arrived patients.