論　文　要　旨

A cluster-based basket trial design in oncology
(バスケット試験におけるクラスタリングに基づく階層ベイズモデルアプローチ)

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As the DNA sequencing technology has developed, the novel clinical trial designs such as basket trials to try for precision medicine has been made to be conducted efficiently in oncology. A basket trial in oncology includes in patients bearing several types of cancers with a common biomarker and evaluate efficacy of treatment in each subgroup. In phase II basket trials, traditional analyses such as Simon two-stage design (Simon, 1989, Controlled Clinical Trials) and Bayesian adaptive design (Thall and Simon, 1994, Biometrics) have been independently applied, which leads insufficient power because of small sample sizes. A Bayesian hierarchical modeling (BHM) has an attractive feature of stabilizing the estimate of treatment effect in each subgroup to borrow the information among subgroups (Thall et al., 2003, Statistics in Medicine; Berry et al., 2013, Clinical Trials). However BHM bears the risk of arbitrariness to determine the degree of shrinkage and the similarity of treatment effect between subgroups. Furthermore the traditional BHM approach is applied in all subgroups, which is undesirable when the heterogeneity of treatment effect is large.

In order to address the issue, our research proposes a new BHM approach for assessing the heterogeneity of treatment effect and estimating treatment effect in each cluster that the subgroups with similar treatment effect belong to. The proposed method quantifies the similarity of treatment effect between two subgroups based on the Jensen-Shannon divergences evaluating the similarity between two probability distributions and groups the subgroup by applying the aggregative hierarchical clustering based on Jensen-Shannon divergence. Subsequently, we evaluate treatment effect in each cluster using BHM. In addition to the BHM analysis, via simulations, the proposed method determines the required sample size in each subgroup and the threshold for determining the optimal number of clusters while maintaining the family wise error rate and marginal power at a certain level. The sample size and thresholds are determined to accomplish the target marginal power and familywise error rate and maximize utility function about marginal power and the expected sample size.

Through simulated studies, to compare to the other Bayesian methods including independent method and BHM approach with weak or strong information borrowing, our proposed method showed inferiority to inflate the mean square error and superiority to maintain the target marginal power and control the false positive rate in each subgroup.