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Editorial

Adaptive Design

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Adaptive design is a special design method. It has become more and more popular in clinical trials and drug development. Adaptive design could use accumulating message to modify the ongoing trial without undermining the validity of the clinical trial, to timely detect and correct some unreasonable assumptions of the experimental design at the start, and to reduce total cost and shorten the time for clinical research(1,2,3) .

Generating background

Currently, traditional trials and drug development trails use parallel contrast design to observe the clinical effect of the drugs, which assumes that all the participants in the test have equal opportunities. Such clinical trial design is easy to operate and control but costs too much, lacks efficiency, and increases the risk of exposing to dangerous factors. (1,4) Traditional trial designs subjected to ethical constraints because they can't match effective treatments with specific subgroups of patients, especially in the clinical drug trials for treatment of cancer and acquired immune deficiency syndrome (AIDS) etc. (2,5,6)

Types and rules

Adaptive designs commonly used in clinical trials include 10 aspects: adaptive randomization, group sequential design, sample revaluation, non-inferiority treatment group eliminating, dose-finding scheme, bio-marker guided randomization, conversion of adaptive design, assumption of adaptive design, seamless designs of phase II/III and multiple adaptive design（7,8）Basic rules of clinical adaptive design include allocation rule, sampling rule, stopping rule and decision rule. (8,9）

Application and Implementation

The long process of a clinical trial and drug development includes four different phases (I to IV trials) with escalating costs, hardly to be acceptable by patients because of the risk of losing one's life or suffering from some rare diseases. For the clinical trial of a multiple myeloma's drug， clinical trials are traditionally conducted in phase I trial that identifies the maximum tolerated dose, and consider it as a basis of testing dosage. This method can't provide the dose range of participant responses. (10) In fact, the study can set multiple dose groups, for example, parallel dose groups, individual or cumulative dose groups, and the research may allow for early stopping of the trial for toxicity, futility or costliness by using Bayes' theorem. As for the phase II/III trials, it also can be achieved to discard bad effect groups as well as to enroll new patients of best treatments by using a seamless phase transition. Thus, it may be translated to greater success rates in such clinical trials with similar funding. (1,11)

Because there are a lot of bias on the type I error rate, we need to ensure the integrity and validity of the trial. Considering the following questions when making adaptive design: 1) Is it necessary to make adaptability designs? 2) What is the difficulty and benefit level? Whether un-blinded does leads to a bias in the assessment of treatment? 3) Does it extend the time to study? 4) Whether the delay in response will reduce the benefits of adaptive design? 5) What is the un-blind frequency? 6) How about the interfering to the decision making by data management committee? 7) Is there any destruction to randomicity? (7,11)

Advantages and disadvantages

Unlike traditional trial designs, the adaptive clinical designs have potential advantages of improving the flexibility, reducing total cost, shortening the time for development and efficiency of clinical trial conduct. Adaptive clinical trial designs hold great promise for improving the efficiency of clinical trials; it helps to end experiments that have insufficient of safety, efficacy and rationality as early as possible in the med-term analysis. Thus, adaptive design can not only help reduce the unnecessary risk, but also provide greater benefit to the subjects in clinical trials during the process. (1,6,12)

Adaptive clinical design depends on the existing data of clinical trials which introduces the operating error, such as the selection bias, evaluation method bias, revision bias, confidence interval of treatment effect error, data collection bias, changes of patient selecting criteria and grouping, hypothesis and statistical contradiction. (11,13)

Cases

We introduce two recently conducted randomized adaptive clinical trials: BATTLE trial and ISPY-2 trial.

The BATTLE (Biomarkers-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination) trial is a phase II trial, enrolled 255 patients with advanced stage IV non-small cell lung cancer. (14) Four different biomarker profiles were used in the trial: EGFR , KRAS and BRAF, VEGF/VEGFR, Cyclin D1/RXR, corresponding to four different targeted drugs: erlotinib, erlotinib plus bexarotene, vandetanib, and sorafenib. The primary aim of the trial was to test the effectiveness of therapy, and to evaluate the predict roles to patients in the trial based on their biomarker in providing better outcome. The result reveals that 8-week disease control rate was 46%, confirmed the hypotheses, and showed a clinical benefit from sorafenib among enrolled patients with mutant KRAS. (2,14)
The ISPY-2 trial is also a phase II trial in the patients with breast cancer. (15) The primary aim was to determine the pathologic complete response (PCR) at the time of surgery. The patients were assigned into ten multiple-arms, depending on hormone-receptor (HR) status, HER2 status and Mamma Print signature. The ISPY-2 trial demonstrated that the combination with carboplatin and veliparib added to pre-surgery chemotherapy could improve the tumor response rate of triple-negative breast cancer. (15,16)
Both trials reduced the cost of drug development, accelerated the process of drug screening, and made the clinical trials more efficiently.

Summary

Well planned and carefully conducted clinical trials that use adaptive designs is necessary because of the complexity and uncertainty of clinical trials and drug development, as well as technical bias and ethical constraints. Adaptive clinical design with undermining the integrity, scientific and validity of the trial can accelerate the course of new drug development.

Conflict Interests Disclosure

The authors have no conflicting interests to disclose.

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