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Phase II clinical trials: issues and practices

Editorial

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Most of the Phase II trials are conducted for evaluating the efficacy of cancer treatment and advancing it to Phase III studies. The future progress in improving cancer therapy can be expedited by better prioritizing the options for Phase III evaluations. Phase II trials, historically, have been key in this prioritization process. Relevant trial designs that have been used include Phase II selection designs, randomized phase II designs that include a reference standard-treatment control arm, phase I/II designs, phase II/III designs. The keys issues in these study designs are:

i. Selection of historical control
ii. Heterogeneity
iii. Adaptive signature design
iv. Randomization (choice Phase II versus Phase IIb)
v. Balancing randomization while maintaining the expected sample size in the phase II clinical studies
vi. Monitoring for futility
vii. Monitoring for toxicity

The phase II clinical study is intended to explore the effectiveness of the new treatment on patients with the disease of interest. The phase II trials inform the decision for the treatment to proceed into the more resource intensive phase III trials. The trials are characterized by relatively small sample sizes, usually around 50-200 subjects. An interesting option of these trials is the single arm design, based on the use of historical controls. Historical controls play a crucial role in selecting the design parameters and identifying the need for randomization. Many times in a rush to move the drug quickly through the pipeline, there is not much emphasis given to carefully evaluating the findings from historical controls. For example, an exciting result from a small study should not be the solely deciding factor for determining the design parameters for the next phase of the study or even replicating another phase II study. Similarly, a large study with negative/weak results should not discouraged just based on the primary findings; a further statistical evaluations in subsets can be used before planning another study or abandoning the current study all together.

In the presence of heterogeneity, not only historical control data can be misleading but also can lead to missing the opportunity for a promising treatment. Barnes & Rai[1] outlined how to model heterogeneity in a single arm Phase II study. Rather than ignoring it, it should be evaluated and accommodated in a simple or randomized study. Extra-variation models can be utilized.

The heterogeneity may depend on some specific characteristics of the cohort, such as clinical factors and gene signatures. If there is systematic response patterns related to phenotype or genotype information, as suggested by Freidlin et al.,,[2] the 'adaptive signature designs' can be used in a phase II trial. In the first stage one can find the gene signatures and then either design two single arm studies or just use the most beneficial group of patients identified based on the gene signatures.

In some instances, the phase II study may be broken up into two sub-phases often referred two as Phase IIA and IIB. Each of the sub-phases are intended to address different primary objectives associated with the new treatment, which when combined, are too complex to be addressed in one trial. The phase IIA is often designed to explore the efficacy of the new treatment while also examining the safety in multiple stage single arm studies. The phase IIB is sometimes referred to as the pivotal trial since a decision must be made to proceed into Phase III testing. The phase IIB is more rigorous study often employing multiple arms to demonstrate the treatments efficacy and safety as well as determine appropriate dosing amount and/or frequency. It is important to note that the phase IIB is not intended to replace the confirmatory phase III trials.

The earlier phase IIA designs are often single arm studies that compare the results to a historical control group. The design parameters for the historical control group can be derived from literature or previous experiences with the disease within the research center. The studies are often easier to conduct requiring fewer patients and less time than randomized studies since they typically measure a binary response and are single arm studies.[3] It is often easier to recruit subjects since they are guaranteed to receive the active treatment. Physicians also find this appealing since the risk of receiving the placebo/control treatment through randomization is removed. Unfortunately, the selection of the historical control is problematic due to several reasons. For instance, the patient populations represented by the studies may not be the same resulting in difference in response rates attributed to the treatment instead of the underlying differences in the population. The single arm studies also assume homogeneity of the population to make statistical inferences but homogeneity is not guaranteed. Barnes & Rai[4] examine the impact of subgroups which create heterogeneity in the response on the operating characteristics of the Simon 2-Stage design.[5]They find that the traditional design has higher than expected type I and II error rates resulting in false negative and false positive phase II outcomes. There are other concerns of bias as well in the single arm phase II trials such as the point estimate of the response under the null hypothesis used to develop the clinical trial design.

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The solutions to some of the above problems are available through randomization which results in the implementation of the phase IIB clinical trial. Typically, the randomized multiple arm-studies still examines the data in a group sequential nature or after a specified number of patients is enrolled. The randomization is often done using stratified procedures to balance the arms on a limited number of characteristics which may be associated with the outcomes in an effort to reduce patient heterogeneity. The outcome is often a binary outcome but incorporate multiple levels of response such as complete or partial response in the oncology setting. The odds ratio is a very convenient way to compare the outcome between several arms in the multiple stage setting. The stopping boundaries used in the group sequential designs ignore the stratification while the analysis includes the stratification. Srivastava et al.,[6] examine this situation in detail and discover that the stratified approach offers consistently better results when the weighted average of the response probabilities across strata between the groups remain close to the hypothesized values, regardless of the differences in response distributions and heterogeneous response rates. The proposed study could be underpowered if the response probabilities deviate significantly from the hypothesized values so the difference in the weighted average is less than hypothesize value.

The purpose of the randomization can fall into one of three broad categories. The patients can be randomized to two or more treatment arms but the treatments arms are not directly compared to each other. Instead, each arm is assessed against predetermined efficacy boundaries in essence running several phase II single arm-trials at one time with the goal of controlling some bias through the randomization process[7]. The second type of randomized phase II trial was first proposed by Simon et al.,[8] to select the most promising treatment (i.e. dose and/or frequency) from several possibilities to proceed into the phase III trial. The third general type of randomized trial is non-definitive comparative trial against the standard treatment. This design is a not a replacement for the confirmatory phase III trial but rather a tool to identify both promising treatments as well as non-promising treatments.[9]

Monitoring of safety in Phase II studies has received very little attention. Simon's[5] single arm trial with two stages has the stopping rules only for futility. It is rare that in a phase IIb (randomized trial) toxicity or/and efficacy are monitored, which is often required in phase III studies. However, it is becoming common to monitor for safety due to combining of immune based therapy in addition to chemotherapy for cancer treatment. We recommend that all phase II trials must incorporate stopping rules for safety as well as for futility. This also becomes imperative since the safety evaluation in phase I trials is based on a very small sample size. The typical approach for monitoring safety is to develop ad-hoc rules that are determined outside of the proposed design for assessing clinical response. This concept was expanded for continuous toxicity monitoring by Ivanova et al.,[10] so the toxicities can be monitored after each patient is treated. The ad-hoc approach assumes the toxicity rate and the response are statistical independent of each other, which is not a valid assumption in most settings. As the correlation between the toxicity rate and the response increase, the trials actually become more conservative or the observed type I error rate is much lower than the specified rate used to propose the sample size. Ray & Rai[11–13] extended the research on multiple stage, multiple endpoint designs. Guidelines as outlined in Ray & Rai[11–13] for monitoring toxicity are very helpful for generating reports that would be helpful to Data and Safety Monitoring Committees.

The research in phase II clinical trials attempt to solve practical problems encountered in the research and development cycle of the modern cancer treatment. The phase II clinical trial is still a screening or early examination of the new treatment before confirmatory phase III trials but the designs are becoming more sophisticated to protect the patients and preserve resources.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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