ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Controversies in the Design of Phase II Clinical Trials

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H&O What are the challenges of current phase II trials, and why is there a need to update the traditional goals of phase II testing?

LS The major limitation of traditional phase II trial designs is that they were developed for drugs that result in rapid tumor shrinkage (objective response). Drugs that had high rates of response, higher than that of known active agents, were usually proven to be effective (ie, prolong survival) in later phase III studies, whereas agents with low response rates were considered inactive. Newer molecularly targeted agents, although they can result in survival benefit for patients, often have relatively low response rates. Teasing out what is an interesting (but low) response rate, and what response rate should stop further clinical development, is thus difficult. Larger studies, especially randomized ones, allow more robust decisions to be made, but are more costly in terms of patients required, resources, and time.

Numerous phase II clinical trials are testing combinations of new drugs with standard treatments. In this type of situation, it is often difficult to determine whether there is any incremental benefit of adding a new drug, especially when it is not expected to substantially increase the overall response rate. In part because of this lack of clarity, many phase III studies are proving to be negative.

H&O What should be the ultimate goals of phase II trials?

LS The goal of phase II trials is to identify promising agents for further study. We need more efficient trial designs, especially when we have a plethora of new drugs that require testing. Investigators need to carefully consider the most appropriate endpoint for the trial, as well as the use of randomization, while also ensuring efficiency. Adaptive statistical designs should be considered in order to achieve this.

Another goal is to figure out a way to run a robust, well-powered, randomized study that will result in accurate data but with minimum cost and resource usage. Currently, this is where much of the discussions of adaptive designs and novel methodologies are emanating from. As a result, investigators are torn between developing a drug that does not work and patients' unmet need for new effective drugs.

H&O What are some alternate endpoints that are being explored?

LS Endpoints such as looking at response as a continuous variable, progression-free survival, patient-reported outcomes (PROs), imaging endpoints, and biomarker-based endpoints are of interest and are actively being explored and validated. PROs are relevant secondary endpoints, particularly in diseases such as prostate or pancreatic cancer, especially with larger and/or randomized trials. Prognostic/predictive markers are also being investigated in phase II trials. The conundrum is whether accrual should be limited to a certain subset of patients

defined by a biomarker. Although there are some examples where the biomarker is clearly validated, and the inclusion of a biomarker-selected group is appropriate, this is usually not the case. The inclusion of unselected patients in phase II trials is then preferable, but it is recommended that the study be adequately powered to answer the question in the cohort of patients with the putative biomarker.

H&O What are the downsides to including imaging and biomarker-based endpoints and PROs in phase II trials?

LS Cost, as well as increased resources and potential delays in accrual and conduct of the trial, are always of concern when trials become more complex. Ensuring that the design and endpoints are carefully chosen and justified, and that all endpoints are validated and qualified before their inclusion, minimizes these risks.

Table 1. Clinical Trial Design Task Force Recommendations for Choosing the Appropriate Primary Endpoint

The first and critical decision point for the design of a phase II trial is based on the choice of the most appropriate primary endpoint, which should be tailored to the disease and drug(s) under investigation.

- Response-based endpoints, such as those defined by RECIST, are standard, especially in early phase II trials. Other qualified biomarkers, such as molecular imaging or tumor markers, may be appropriate in select circumstances. Response-based endpoints are appropriate primary endpoints if unambiguous and clinically relevant direct anti-tumor activity (such as tumor shrinkage) is hypothesized.
- If a response-based endpoint is not appropriate, especially in later phase II trials, progression-free survival is recommended as the primary endpoint. Other biomarker endpoints (such as tumor burden, tumor markers, novel imaging, tumor response, molecular biomarkers) and patient-reported outcomes are always encouraged as secondary endpoints, especially in the context of studies that aim to qualify such endpoints. It is acknowledged that once qualified, these biomarker endpoints will become appropriate primary endpoints.

H&O What is the Clinical Trial Design Task Force and what is its role?

LS The Clinical Trial Design Taskforce of the Investigational Drug Steering Committee (IDSC) of the National Cancer Institute Cancer Therapy and Evaluation Program advises the IDSC on trial design of early clinical trials. As part of this mandate, 2 workshops and resulting recommendations have been coordinated, one addressing phase I design and the other phase II design. The consensus recommendations are presented in Tables 1–3.

Table 2. Clinical Trial Design Task Force Recommendations for Study Design

Study Design: Primary Endpoint is Tumor Response

- ***Monotherapy trials***
  Single-arm designs are acceptable. However, randomization should be encouraged to optimize dose and schedule or to benchmark activity against known active therapies.
- ***Combination trials***
  With some exceptions (eg, availability of a well validated, robust control database), randomization is usually required for trials testing combinations of agents to establish efficacy. An example is standard therapy plus/minus novel agent or combinations of novel agents.

Study Design: Primary Endpoint is Progression-Free Survival

- ***Monotherapy or combination trials***

1. With some exceptions (eg, availability of a robust control database), randomization is required
2. For randomized trials, blinded designs are encouraged where feasible. While placebo controlled trials are challenging, they are encouraged whenever possible. Alternatives include dose ranging, randomization vs active controls or other novel agents, and randomized discontinuation and other crossover designs.
3. It may be informative to prospectively incorporate crossover to the standard therapy plus novel agent for those patients initially assigned to standard therapy alone, although careful consideration should be given to the timing of crossover (eg, only after the primary endpoint has been observed). Such cross-over designs increase the access of patients to investigational agents, and also provide additional information about the activity of the study arms.

Table 3. Clinical Trial Design Task Force Recommendations for Patient Selection and Enrichment Strategies

Monotherapy or Combination Trials

1. A goal of phase (I and) II development should be to define biomarkers predictive of efficacy and/or toxicity. Where feasible and appropriate, molecular biomarkers should be explored in order to identify subsets of patients of interest for future study.
2. Enrollment should in general not be limited by biomarker status unless there are strong confirmatory and supportive clinical data justifying the enrichment strategy. Adaptive statistical designs may be used to allow modification of enrollment if data suggest a biomarker is predictive.
3. In an unselected trial (ie, patients not defined by a biomarker), the patient population of primary interest (ie, a cohort defined by a biomarker) should be predefined and the study powered accordingly to detect an effect in that subset.
4. Multi-disease phase II designs should be considered, especially if the objective is to test a biomarker-focused hypothesis.

Statistical Designs

- Prospective designs that adapt to what is learned during the trial can improve the efficiency of drug development and provide greater precision.
- Available adaptations include stopping early, continuing longer than anticipated, dropping arms (or doses), adding arms, focusing on patient subsets, assignment of better performing treatment arms with greater probability, and seamlessly moving from phase I to II or phase II to III during a single trial.

H&O Some argue that phase II trials should be eliminated. What is your stance?

LS Our goal should be to get the best drug in class licensed and available to patients, and for this it is necessary to have some kind of screening mechanism given the large number of new agents. Phase II trials are screening trials to identify promising drugs and to weed out ineffective therapies. It is not feasible or reasonable to conduct phase III trials for all new agents. However, timelines can be optimized by using adaptive designs or seamless phase I/II or phase II/III studies. Although some investigators have suggested that phase II studies are of limited value and serve only to delay definitive trials, I believe they have an important role in early drug development, performing a screening function and allowing better definition of toxicity, dose, and schedule.

Suggested Readings

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