

Early Phase Clinical Trials

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Learning Objectives

1. Understand clinical questions of interest
2. Understand statistical questions of interest
3. Understand different phases (0/1/2)
4. Able to discuss designs for early phase clinical trials



My Background (biases)

- Department of Oncology (associate appointment with Clin Epi & Biostats)
- 9+ years in cancer clinical trials
- Primarily phase I or II
- Very little involvement with other diseases



Background

- Does anyone have experience designing an early phase trial?
- What would you consider to be an early-phase trial?
- What are the study objectives?
- How do they differ from a late-phase trial?



Phase I

•**FDA Definition:** Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and may be conducted in patients, but are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies



Phase II

•**FDA Definition:** Phase 2 includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred people.



Clinical Trial Phases

•NIH Definition:

PHASE I TRIALS: Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients.

PHASE II TRIALS: Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.

PHASE III TRIALS: Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling.



Scenario

- You are working for a pharmaceutical company who has developed a new agent
- Wish to set up plan for testing agent
- Company needs to plan long-term outlook (to discuss at annual stock owners meeting)
- Aim is to ultimately get regulatory approval



As a company executive, what do you need to know?

- What disease?
- What is likelihood of approval?
- How long to get approval?
- What is the competition?
- How is the new agent different from others?
- What is the cost to make?
- What will the likely profit be (how much can you charge)?

As a clinical lead, what do you need to know?

- What are the standard treatments?
- How effective/toxic are standard treatments?
- How does one define efficacy?
- What evidence do regulators need to approve agent?
- How is agent administered?

As a scientist, what do you need to know?

- Pre-clinical (lab) work
- Has it been studied in animals?
- What animals? What is known relationship to humans?
- What is results of lab work?
- How does agent work (pharmacokinetics/pharmacodynamics)?
- how does it get to blood stream, how much gets to system, how does it get out of the system

As a biostatistician, what do you need to know?

- All of the above
- What are typical designs?
- How many trials do you think will be needed prior to ultimate approval?

Clinical Trial 1

- What question should be answered in first clinical trial?
- Is it safe to administer? Is there any biological activity? How much should we give?
- Give to small number of humans in a controlled environment (why?) and check (side) effects
- Should one escalate dose – intra/inter (why?)
- Would also like to get scientific data (pK/pD, hitting target)
- Volunteers or patients?
- Do you get any information on efficacy?

Phase I: Cancer (3+3)

- Give to 3 patients
- If 0/3 have dose limiting toxicity - escalate
- If 1/3 has DLT, expand to 3 more patients
- If 1/6 has DLT – escalate
- If $\geq 2/3$ or $\geq 2/6$ – reached maximum tolerated dose
- Recommended phase II dose is the dose below MTD
- Europe: MTD=RP2D
- DEFINE!!!!!!

Dose Levels

- DLT: serious or life-threatening AE occurring in first cycle – not standard
- DL1 usually based on animal data (e.g. 1/10th LD50 in mice)
- Escalation of doses uses Fibonacci sequence
- Oral medications: based on availability of doses (i.e. if only come in 50 mg pills)
- Problems with this design?
- Positives about this design?

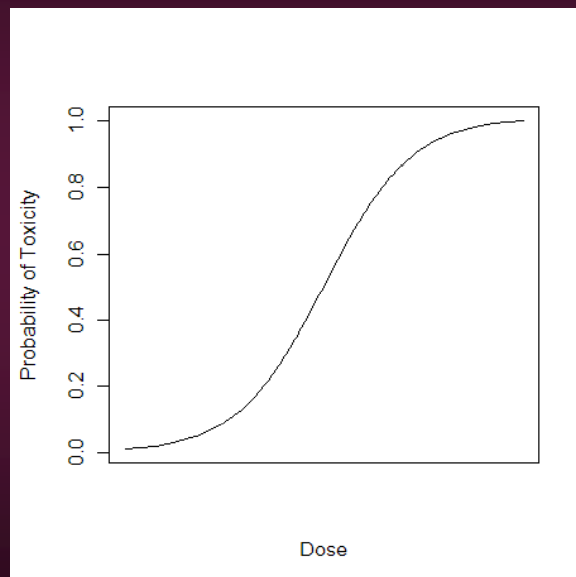
Comments

- Often start 'too low' for safety reasons, but limits possibility of activity
- Phase I response rates quoted as ~5% - minimal practical benefit (hope)
- Patients do not enter these trials altruistically
- Patient survival in months
- Long-term toxicities?

Modified Designs

- Rapid early escalation and intra-patient escalation permitted
- 1 pt / dose level until grade 2 AE, then 3+3
- Bayesian designs: estimate dose-toxicity curve or probability of SAE at dose level
- Reduce # of patients in trial (slightly), may improve dosing accuracy, no improvement in total trial time

Example dose-toxicity curve



Phase I: Non-cancer

- Give dose to paid volunteers
- How much would you need to be paid to take a drug with a 33% chance of giving you a serious/life-threatening AE?
- What is compensation if 33% of volunteers get SAE?
- Most treatments expected to have few/none AE

Phase I: Non-cancer

- How do you measure safety/outcomes?
- Measure the effects on body (pharmacokinetics, pharmacodynamics)
- Ensure it is within acceptable limits
- Statistical tests on differences in variability
- Differences in mean less important (why?)
- How do you define maximum dose?

Trial Designs

- Small numbers needed (30-60)
- Outcome is variability
- Practical issue – cost required to pay volunteers
- Short term dosing – some drugs required to be used long-term (anti-hypertensive, anti-diabetic, arthritis)
- Accuracy of identifying proper dose critical

Phase II

- Is there any evidence of activity?
- Might this agent be potentially useful?
- Do not want to test if drug is 'better' than standard treatment (why not?)
- Should the drug be tested in a further trial, comparing it with standard

Phase II: non-cancer

- Compare efficacy – often of a surrogate outcome
- Small, randomised trial – often will find a large effect
- Does blood pressure go down – surrogate for OS
- Do MS patients improve activity levels, walk? – long-term abilities
- Does hand strength improve in arthritis pts – number of days without knee pain
- Placebo-controlled due to placebo effect

Phase II: non-cancer

- Size – few hundred to few thousand
- May be able to get regulatory approval
- Different doses, dosing strategies may be tested
- Multiple comparison adjustments
- $\alpha=0.05$, $\beta=0.80$ or 0.90 (what will you do after study is complete?)

Phase II: non-cancer

- Trial design: standard statistical analyses
- T-tests, χ^2 tests, Wilcoxon rank-sum, Fisher's exact tests
- Estimation of differences also important
- Some subgroup analyses performed, though power is small – pre-define

Phase II: Cancer

- Placebo generally considered unethical
- Any disease which is terminal, or requires intervention of some sort (schizophrenia, HIV)
- Best supportive care may be given for palliation
- How would you measure if there is 'any evidence of activity'?
- Most cancer drugs historically fail and have substantial side effects (33% have serious/life-threatening AE in 1st 28 days alone)

Phase II: Cancer

- Give to small numbers of patients (single-arm)
- If any evidence of activity, give it to a few more patients
- If sufficient numbers 'respond' – i.e. tumour shrinks – treatment is worthy of further study
- Two stages (adjust CI for interim analysis)
- Many questions about adequacy of this design (like what?)

Questions

- Often novel therapies are given in addition to standard of care (i.e. std + trt) with some baseline level of activity
- What if treatment designed not to shrink tumour, but only prevent it from growing?
- How comfortable would you be launching a \$10M, 1000-patient study after only 3 responses in 30 patients?

'Novel' designs

- Randomised phase II
- Use time-to-progression/progression-free survival as outcome and compare
- >4x number of patients needed
- Solutions: look for massive effects, inflate α and β
- One suggestion is $\alpha=0.20$, $\beta=0.20$, HR=0.6 – unrealistic
- NOTE: PD only measured at fixed time points (e.g. every 56 days), and median TTP/PFS often small

'Novel' designs

- Randomised discontinuation trials
- Treat all patients with agent for 1 cycle
- Keep treating patients with a response
- Stop treating patients who are progressing
- Randomize patients with stable disease to treatment versus placebo
- Primary analysis is comparison of randomized patients
- Re-challenge placebo patients who progress
- Ethics? # of SD patients?

Actual Trial

- Randomized trial comparing trt A versus best supportive care
- If BSC patient fails, crossover patient
- i.e. treat with A (all patients eventually get A)
- Primary outcome is time to progression
- Key secondary outcome is overall survival
- Problems?

'Novel' designs

- Randomised selection trials
- Randomise to 2 or more treatments
- No formal statistical comparison
- 'Pick-the-winner' for phase III study
- Problems?

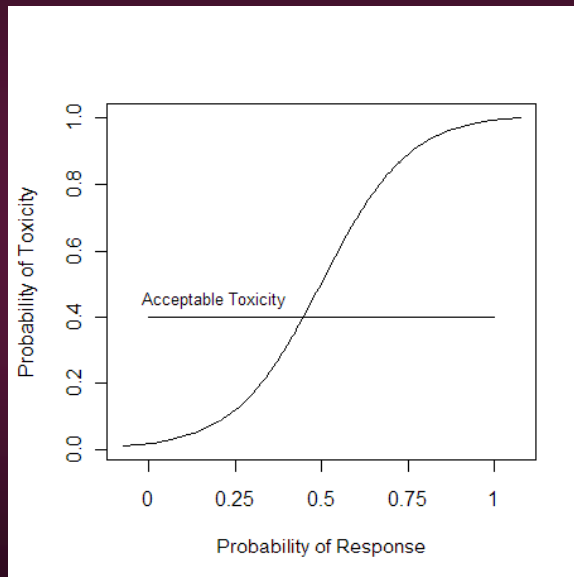
'Novel' designs

- Randomised non-comparison trials
- Randomise to 2 or more treatments, 1 is standard of care
- Suggested when unsure of H0 of standard
- No formal comparison between arms, may have a 'visual check'
- Use traditional design for analysis of novel therapies
- Standard of care arm to 'validate' H0
- Problems?

Combined Phase Trials

- Combined phase trials
- Phase I/II trials
- Include phase I patients in phase II analysis
- Only if treated in same dose, same disease, same population
- Bayesian: response-toxicity curve
- Works well if curve correctly estimated
- Not so sure works well in molecularly targeted agents

Bayesian Response-Toxicity Curve



Combined Phase Trials

- Phase II/III
- Do randomised phase II study using a surrogate endpoint
- Stop at analysis 1 if lack of efficacy
- Continue to phase III if some evidence
- Does not affect the α
- However, must be willing to commit resources for larger study
- Will prevent study in other agents

Phase 0

- What do you think they are?
- Looking for biological effects only
- E.g. Give as a single-agent for 1 week/day
- Evaluate biological markers (target activity, pK, pD)
- Then do regular study (agent+chemo)
- 1st week evaluation expected to have no clinical benefit

Phase 0

- Preferentially given as part of phase I study (can identify dose effect)
- Not necessarily given to all patients in study
- Occasionally given in isolation (give 1 month of treatment to 5-10 patients)
- No benefit to patient (even if they respond, treatment is withdrawn), possible harm (AE), increased incursion at end of patient life
- Ethics?
- Recruitment of patients?

Additional Considerations

- Ethics – much more complex than phase III
- Benefit to patient is of concern – can not overstate in ICF
- Considerable risk of harm
- Small numbers of patients
- Cost of novel therapies – if effective, may get regulatory approval, but will it get funded?

Additional Considerations

- Logistical complexities
- Scientific questions may require substantial patient involvement – is this reasonable?
- What about when patients are nearing end of life?
- How many blood samples is reasonable?
- How many biopsies is reasonable (skin versus lung)

Additional Considerations

- QOL studies
- Requires completing questionnaires
- How do you involve patients who speak different languages, have cognitive deficits?
- Do you incorporate a financial analysis in study? More complexities

Additional Considerations

- Duration
- Phase I and II are supposed to be 'quick'
- Can take 2-3 years (or more) each
- What will landscape look like in 10 years (when applying for regulatory approval)?

Final thoughts

- Early phase studies often have 'simple' designs
- More complex/issues than late stage designs
- Must factor in many non-statistical issues in analysis, design, interpretation, inference
- Must, as a biostatistician, have understanding of non-statistical aspects, and
- Must be able to communicate effectively with non-statisticians (clinicians, nurses, CRA, ethics, regulatory, pathologists, radiologists, lab technicians, scientists, IT, geneticists, ...)