Clinical Trial Design

Definition

“Clinical trials are a special kind of cohort study in which interventions are specifically introduced by the investigators in ways that improve the possibility of observing effects that are free from bias”

Retrospective vs Prospective

- **Retrospective**
  - Gather data on historical cases. Limited by data collection, lead-time bias, temporal bias, yadda yadda
  - Generates questions, NOT answers (way too much bias)
  - Results should only rarely alter standard of care
  - Unfortunately, much of our S-of-C in Vet Med based on retrospective analysis
- **Prospective**
  - Compare 1 population to another by entering patients as they are seen and using predetermined allocation procedures to control bias

Basic Clinical Trial Structure

Purpose of clinical trials

- Ultimate goal: The need to improve “standard-of-care”
- Determine dose and toxicity profile of a new drug/procedure
  - “Phase I trial”
- Determine “efficacy/activity” of new drug/procedure
  - “Phase II trial”
- Is it better than current treatment
  - (“comparative trial” or “Phase III trial”)
- Gather ancillary data (prognostic and predictive factors)
- Inform human clinical trials

Bringing a new anticancer drug to market … several phases
Who enters phase I

- Refractory to standard-of-care
- Often heavily pretreated and poor performance scores
- In veterinary trials, who enters a phase I?
  - No standard-of-care exists
  - standard-of-care sucks
- Financial constraints on standard-of-care
  - Offset treatment costs
  - Additional incentive for alternate therapy at failure
  - Altruistic?

Setting the Initial dose level

- Weigh toxicity probability against efficacy
  - Too low starting dose results in prolonged trial, poor utilization of resources, and ethics of using sub- efficacious doses
  - Normal volunteers - 1/10 NOAEL
  - Not the case in cancer trials, rather 1/3 NOAEL
  - Patient advocates - patient can choose their starting dose
  - If normal dog tox known, then 50% of MTD
  - Beagles are not cancer-bearing dogs
  - Typically, if no normal dog, then 10% of the LD10 of rodent or other species

Dose Limiting Toxicity

- a dose-limiting toxicity (DLT) is defined as a Grade III toxicity in any category except hematologic
- Grade IV used for hematologic toxicity
- use Veterinary Cooperative Oncology Group Common Terminology Criteria for Adverse Events (VCOG-CTCAE) v3.0.

Phase I Trial = “Toxicity Trial”

- Goal is to determine the MTD (maximally tolerated dose) for future phase II
- Elucidate parameters of toxicity
- Schedule and route
- Secondary goals
  - PK/PD issues (ADME)
  - Target modulation
- Efficacy is NOT a primary goal, but nice to see. Average response rate is <10% in phase I trials.
- Increasing dose in Cohorts of 3 is typical (3 + 3 design)
Dose escalation strategies

- Increments:
  - Fixed-dose modified Fibonacci
  - Accelerated titration - small patients, dose increased by factor of 2 if a grade 2 toxicity occurs, then more typical acceleration
  - Those < 6 of patients treated at doses far from the MTD
  - If myelosuppression prime toxicity, then can base dose escalation on degree
  - PK-based strategies
  - Target modulation strategies
  - Continuous reassessment methods
  - Always a trade off of risk versus benefit

Table 1: Modified Fibonacci Dose Escalation Scheme

<table>
<thead>
<tr>
<th>Dose</th>
<th>% Increase above previous dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>100</td>
</tr>
<tr>
<td>2.5X</td>
<td>100</td>
</tr>
<tr>
<td>5X</td>
<td>87</td>
</tr>
<tr>
<td>7.5X</td>
<td>76</td>
</tr>
<tr>
<td>10X</td>
<td>68</td>
</tr>
<tr>
<td>15X</td>
<td>60</td>
</tr>
<tr>
<td>20X</td>
<td>55</td>
</tr>
<tr>
<td>30X</td>
<td>50</td>
</tr>
<tr>
<td>40X</td>
<td>45</td>
</tr>
</tbody>
</table>

MTD vs BOD

- MTD may be irrelevant for new so-called static drugs or targeted drugs
- The dose that maximizes the target modulation would be the end-point
- Could use validated surrogate assays

Phase II = “Efficacy trial”

- Goal:
  - Using the MTD/BOD from phase I, identify the clinical or biologic activity (i.e., which tumor types respond)
  - Standard single-arm study
    - Treat a minimum of 9 of each tumor histology or target population (this keeps the likelihood of a false negative result to 80% [type II error]
    - If 1 responder, then > to 31 patients to get accurate response rate
  - Treat more if expecting lower response rate
  - Estimate therapeutic index
  - Expand toxicity data (e.g., cat doxil and renal toxicity)
Are all errors created equal?

- **Old school**: Consequence of type I error (false positive) is less deleterious than type II error (false negative) as false positive trials are likely to be repeated versus false negative trials may lead to the abandonment of a particular treatment.
  - e.g., Cisplatin
- **New School**: False positives are just as serious due to:
  - >>> # of new agents to investigate
  - High cost $$$ and patient resource cost is so high

Clinical Endpoints

- Other endpoints:
  - Q of L measures (gemzar)
  - Temporal measures for newer agents
  - Time to progression
  - Progression free rate
- Molecular endpoints:
  - Dephosphorylation of growth factor receptor
  - Vessel density
  - Functional imaging

Phase III trials (Comparative Trials)

- Phase II are “learning” trials and phase III are “confirming” trials
- Larger, randomized blinded trials

Only 14% of phase II trials in Oncology are positive

“companies should consider phase II trial designs that are more predictive of phase III success.”

Stopping Rules

- Terminate trial within a predetermined adaptive trial design
- Protect patients from unsafe drugs and/or hasten availability of superior drugs
- 3 reasons to stop:
  1. Investigational drug clearly better than control
  2. It is clearly worse than control (< activity, > toxicity)
  3. It is not likely to be better = “stopping for futility”

Stopping Rules

- Interim analysis by a blinded individual
- Predetermined rules
  - “conditional power”
    - The probability that the final result will demonstrate statistical significance conditional on the current data and assumptions on future data
  - “Stochastic curtailing”

Bayesian (continuous learning) Designs

- Adaptive designs:
  - Can stop trials early
  - Can change randomization weight to better performing arms
  - Can add new arms
  - Extend accrual beyond target
- Frequentist approach
  - Traditional method uses fixed parameters - inflexible
- Bayesian - makes statistical inferences using:
  - Accumulated data
  - Historical data
  - Data from other trials

Bayesian Example

- EGFR2 +ve breast cancer study
- Initial design = 164 patients
- Bayesian approach after 34 patients enrolled
  - 67% CR in study arm
  - 25% in control
  - Bayesian predictive probability of 95% if 164 enrolled so trial stopped and Phase III initiated early

Enrichment

- Intent is to select a subset of patients to enroll that are relatively homogenous with respect to prognostic or predictive factors and randomize only these patients
- e.g.:
  - All start, then randomize compliers/no-tox
  - “drugable” target identification
  - Exclude poor prognostic group
  - Randomized discontinuation

Enrichment example:

- Trastuzumab Her-2 mAb + chemo
- 469 patients needed in study when entering only Her-2 over-expressers (1 yr. OS 78% vs. 67%)
- If unselected patients - 23,586 would have been required to show the difference!
- Problem: what if your wrong about the “target”?
Phase II Trials: Paradigm Shift

- Cytotoxic phase II design: end point is tumor shrinkage (i.e., RECIST)
- Newer putative cytostatic agents slow tumor growth or induce stasis (induction of stable disease)
  - Heterogenous growth rates in patient population lead to problems
  - Some naturally grow very slowly
  - Must distinguish antiproliferative activity of drug from indolent disease process ("no treatment effect")
  - e.g., small molecule TK inhibitors, antiangiogenic agents, metronomic protocols

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According to simulation, expect 70% of patients will progress during the 16 weeks, 0% will regress spontaneously and 30% will be stable.

* If placebo patients progress off drug, code broken and they are switched back to drug.

Note, if high grade toxicity, also removed from trial.

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Sorafenib +ve trial

- RAF kinase inhibitor
- 34% shrinkage of RCC by 12 wks
- 69 patients stable and randomized
  - 50% stayed stable in treatment group
  - 18% in placebo
  - p = 0.0077

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Table 4: Suggested “Elements of Consent” to include in Informed Client Consent documents

<table>
<thead>
<tr>
<th>Element of Consent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Purpose of Research</td>
</tr>
<tr>
<td>2. Expected Duration of Participation</td>
</tr>
<tr>
<td>3. Description of Procedures</td>
</tr>
<tr>
<td>4. Possible Discomforts and Risks</td>
</tr>
<tr>
<td>5. Possible Benefits</td>
</tr>
<tr>
<td>6. Alternatives (for non-clinical or non-participatory)</td>
</tr>
<tr>
<td>7. Sources of Confidentiality of Records</td>
</tr>
<tr>
<td>8. Compensation/Benefits/Outcomes</td>
</tr>
<tr>
<td>9. Contact Person for the Study</td>
</tr>
<tr>
<td>10. Voluntary Participation and Right to Withdraw</td>
</tr>
<tr>
<td>11. Termination of Participation by the Institutional Investigator</td>
</tr>
<tr>
<td>12. Informed Consent</td>
</tr>
<tr>
<td>13. Financial Obligations</td>
</tr>
<tr>
<td>14. Hospital Review Committee/City Process</td>
</tr>
</tbody>
</table>

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