The questions are changing in early phase cancer clinical trials: Opportunities for novel statistical designs

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Outline

○ Classic drug development in oncology research
  ● Cancer treatments
  ● Measuring safety and efficacy
  ● Phase I dose finding for toxic treatments
    ○ Algorithmic designs
    ○ Model based designs
  ● Phase II efficacy evaluation
○ Targeted agents and their implications in clinical trial design
  ● Endpoints of interest
  ● Phase I
  ● Phase II (brief)
  ● Phase 0
○ Moving forward: what should statisticians do now?
Classic Phases of “Drug” Development in Oncology Research

- Preclinical
  - basic science
  - animal studies
  - can take 5 or more years
- Phase I
  - dose finding: identification of the maximum tolerated dose (MTD)
  - often ‘first in man’; often combinations of approved drugs
- Phase II
  - initial efficacy
  - classically, one arm studies; sometimes, randomized
- Phase III
  - large randomized trial
  - head-to-head comparison of new drug (or combination) to the standard of care
Cancer Treatments

- Historically, three primary treatment modalities
  - surgery (resection)
  - radiation
  - chemotherapy

- Depending on disease type and stage, a patient may have any combination of one or more of these approaches
Medical Oncology

- Chemotherapeutic treatments
  - “chemical therapy”
  - can be cytotoxic: kills the cancer cells
  - can be cytostatic: prevents new cells from growing
  - generally associated with being toxic at high doses
  - assumption: as dose increases, both toxicity and efficacy of chemotherapy increase

- Toxic treatments: “poisons” given at doses that kill the cancer but spare the patient
Efficacy and Toxicity Increase with Dose

DLT = dose-limiting toxicity
Measuring Effects in Cancer Trials

- **Phase I: dose finding**
  - Find the highest dose that is deemed safe: the Maximum Tolerated Dose (MTD)
  - DLT = dose limiting toxicity
  - Goal is to find the highest dose that has a DLT rate of $x\%$ or less (usually ranges from 20% to 40%)

- **Phase II: efficacy**
  - Determine if the drug causes the tumor to shrink
  - Clinical response.
    - complete response = 100% shrinkage of tumor
    - partial response = 30% or greater decrease in tumor size
  - Goal is to estimate the response rate (actually, response proportion)
Classic Phase I approach: Algorithmic Designs

- “3+3” or “3 by 3”
- Prespecify a set of doses to consider, usually between 3 and 10 doses.

Treat 3 patients at dose $K$
1. If 0 patients experience DLT, escalate to dose $K+1$
2. If 2 or more patients experience DLT, de-escalate to level $K-1$
3. If 1 patient experiences DLT, treat 3 more patients at dose level $K$
   A. If 1 of 6 experiences DLT, escalate to dose level $K+1$
   B. If 2 or more of 6 experiences DLT, de-escalate to level $K-1$

- MTD is considered highest dose at which 1 or 0 out of six patients experiences DLT.
- **Confidence in MTD is usually poor.**
“Novel” Phase I approaches

- Continual reassessment method (CRM) (O’Quigley et al. 1990)
- Many changes and updates in 20 years
- Tends to be most preferred by statisticians
- Other Bayesian designs (e.g. EWOC) and model-based designs
- Other improvements in algorithmic designs
  - Accelerated titration design (Simon)
  - Up-down design (Storer)
CRM: Bayesian Adaptive Design

- Dose for next patient is determined based on toxicity responses of patients previously treated in the trial.
- After each cohort of patients, posterior distribution is updated to give model prediction of optimal dose for a **given level of toxicity** (DLT rate).
- Find dose that is most consistent with desired DLT rate.
- Modifications have been both Bayesian and non-Bayesian.
Example:

\[
p(\text{toxicity}|\text{dose} = d_i) = \frac{\exp(3 + \alpha d_i)}{1 + \exp(3 + \alpha d_i)} \quad \text{(where } d = \text{dose} - 7)\]

Example:
One-parameter logistic
Classic Phase II trial design

- **Goal:** determine if there is sufficient efficacy to take agent to Phase III
- Binary response endpoint
- **Hypothesis testing based example**
  - null hypothesis: \( p = 20\% \)
  - alternative hypothesis: \( p = 40\% \)
  - select N based on power and alpha
- Simon two-stage design, allows one early look for futility
- Either single arm or randomized phase II.
- *Early stopping considered critically important!*
New paradigm: Targeted Therapy

- Greater knowledge about cancer mechanism
  - GENETICS
  - IMMUNOLOGY
- Example 1: genetics
  - HER-2 positive breast cancer
  - Human Epidermal growth factor Receptor 2
  - “Herceptin” (aka trastuzumab) approved by FDA in 2006
  - It targets HER-2 overexpression which causes cancer cells to grow and divide more quickly
  - approval for use in combination with other therapies
  - about 25% of breast cancers are HER-2 positive
New paradigm: Targeted Therapy

Example 2: immunology

- Cancer treatment vaccines activate B cells and killer T cells, direct them to recognize and act against specific types of cancer.
- There are currently no FDA-approved cancer treatment vaccines.
- But there is a lot of ongoing research:
  - pancreatic cancer: Laheru et al. (2005)
  - breast cancer: Disis et al. (2009)
  - lymphoma: Redfern et al. (2006)
  - (to name just a few)
How do targeted therapies change the drug development paradigm?

- Not all targeted therapies have toxicity
  - Toxicity may not occur at all
  - Toxicity may not increase with dose

- Targeted therapies may not shrink tumors (yet may prolong life)

- Targeted agents may only be effective in patients with specific disease subtype
  - Tamoxifen: Hormone receptor positive breast cancer
  - Gefitinib (Iressa): EGFR overexpressing non-small cell lung cancer (about 10% of lung cancers)
Implications for Study Design

- Previous assumption may not hold
  - Does efficacy increase with dose? (figure)

- Endpoints may no longer be appropriate
  - Should we be looking for the MTD?
  - Should be measuring efficacy by tumor shrinkage?

- Patient accrual will be compromised
  - Subtypes of disease implies smaller number of eligible patients
  - Need incredibly efficient designs!

- Genetic pathways are complicated:
  - Targeted agents may be ‘promiscuous’
  - Limiting it to a genetic subtype may be too focused.
  - How can we define what genes and pathways are associated with response? (figure)
Possible Dose-Toxicity & Dose-Efficacy Relationships for Targeted Agent
Targeted therapy example

- Pancreatic tumor vaccine
  - In preclinical studies, no toxicities and none expected in the clinical setting.
  - How do we determine the dose to take into phase II?
  - What is the “Biologically optimal dose” (BOD)?
    - Not clinical!
    - Examples:
      - T cell response
      - Gene expression/inhibition
Targeted Therapy Example: Current Practices

- ‘3+3’: not modifiable to efficacy outcome
- Compromise:
  - Use 3+3 with toxicity as primary outcome
  - Collect patient tissue to identify biologic outcomes
  - Identify BOD such that toxicity is acceptable
  - Problem? experimental design not geared for identifying BOD
- CRM:
  - designed for targeted level of binary outcome.
  - What if we changed binary outcome to biologic response?
  - Not completely translatable (Zohar and O’Quigley)
  - Requires BINARY measure of effectiveness
Trinary outcome, $Y^*$

- $Y = 0$ if no toxicity, no efficacy
  - $Y = 1$ if no toxicity, efficacy
  - $Y = 2$ if toxicity

- Continuation Ratio Model:
  - $\pi_2(d)$: monotone increasing function of dose $(d)$
  - $\pi_0(d)$: monotone non-increasing function of dose.
  - $\pi_1(d)$ is unimodal and can be either non-increasing or non-decreasing across a range of doses.

\[
\log\left(\frac{\pi_1(d)}{\pi_0(d)}\right) = \gamma_{01} + \gamma_{11}d
\]
\[
\log\left(\frac{\pi_2(d)}{1 - \pi_2(d)}\right) = \gamma_{02} + \gamma_{12}d
\]
\[
\sum_{r=0}^{2} \pi_r(d) = 1
\]
\[
\gamma_{01} > \gamma_{02}
\]

* Zhang et al. (2006), Mandrekar et al. (2007). Thall and Russell (1998); Fan and Chaloner
Continuation Ratio Design
Is this working in the clinic: NO!

- ‘Scientific’ Reasons
  - Lack of biomarkers for efficacy
  - If biomarker available, inability to assess in real-time
  - Desire to test only specific dose-levels
  - Dissatisfied with dichotomous efficacy determination

Slide courtesy of Dan Sargent
Is this working in the clinic: NO!

- ‘Pragmatic’ Reasons
  - Lack of familiarity
  - Discomfort with ‘black box’
  - Loss of control/reliance on statisticians
  - Fear of lack of regulatory acceptance
  - ‘Don’t want to be the first’

Slide courtesy of Dan Sargent
Translation of innovative designs into phase I trials.
Rogatko A, Schoeneck D, Jonas W, Tighiouart M, Khuri FR, Porter A.
We examined abstract records of cancer phase I trials from the Science Citation Index database between 1991 and 2006 and classified them into clinical and statistical trials. RESULTS: 1235 clinical and 90 statistical studies were identified. Only 1.6% of the phase I cancer trials (20 of 1,235 trials) followed a design proposed in one of the statistical studies. These 20 clinical trials followed Bayesian adaptive designs. The remainder used variations of the standard up-and-down method. CONCLUSION: A consequence of using less effective designs is that more patients are treated with doses outside the therapeutic window. Simulation studies have shown that up-and-down designs treated only 35% of patients at optimal dose levels versus 55% for Bayesian adaptive designs. This implies needless loss of treatment efficacy and, possibly, lives. We suggest that regulatory agencies should proactively encourage the adoption of statistical designs that would allow more patients to be treated at near-optimal doses while controlling for excessive toxicity.

Phase II for targeted therapies

- Recall: targeted therapies are often expected to arrest growth but not shrink tumor
- Outcome of interest: time to progression
- Challenges:
  - Takes time to evaluate
  - Measurement is imprecise:
    - Progression is defined as 20% increase in tumor size from baseline
    - Relies on imaging which has measurement error issues (but so does response!)
  - Interval censoring
Interval censoring

- **Time to progression:** time from baseline to 20% or greater increase in tumor size or death
- Patients are evaluated anywhere from every cycle (3-4 weeks) to every 4 months (or more!).
- However, symptomatic progression or death may occur (varying interval lengths)
- Large intervals of time pass so that we do not know when progression actually occurs.
- (Example slide)
- Statistical solution (increased visits) is in conflict with clinical care and patient QoL.
Everolimus in advanced renal cell cancer

Figure 2: Kaplan-Meier estimates of progression-free survival
Adding in a new level: Phase 0?

- “Human micro-dosing”
- First in man
- Not dose finding
- Proof-of-principle
  - Give very small dose not expected to be therapeutic
  - Test that target is modified
- Short term: one dose
- Requires pre and post patient sampling.
- Provides useful info for phase I (or if you should simply abandon agent).
Designing Phase 0 Cancer Clinical Trials
Oncologic Phase 0 Trials Incorporating Clinical Pharmacodynamics: from Concept to Patient
A Phase 0 Trial of Riluzole in Patients with Resectable Stage III and IV Melanoma
Preclinical Modeling of a Phase 0 Clinical Trial: Qualification of a Pharmacodynamic Assay of Poly (ADP-Ribose) Polymerase in Tumor Biopsies of Mouse Xenografts
Phase 0 Trials: An Industry Perspective
The Ethics of Phase 0 Oncology Trials
Patient Perspectives on Phase 0 Clinical Trials
The Development of Phase I Cancer Trial Methodologies: the Use of Pharmacokinetic and Pharmacodynamic End Points Sets the Scene for Phase 0 Cancer Clinical Trials
Phase 0 Trials: Are They Ethically Challenged?
Half the battle

- Addressing the statistical questions is just part of the story
- **Design** methodology differs from **Analytic** methodology in important PRACTICAL ways
  - Designs need to be reviewed by IRBs, scientific review committees, study sections and other regulatory agencies (e.g. CTEP, FDA).
    - 3+3: “we’ve always done it this way!”
    - CRM: “we cant let a computer make our decisions!”
  - Data does not exist for application
  - Time frame for design development is often very short
Adopting new designs

- Serious consideration needs to be given to the audience for novel trial designs
- Clinicians and translational researchers need to be included in the development
  - Need to “get it”, at least superficially
  - Need to be exposed to why it's better
- Need to consider how other statisticians can easily implement these designs.
Challenges for the oncology biostatistics community

- New designs
  - Make them accessible
    - To statisticians
    - To medical community
  - Provide software!
- “Old novel” designs
  - Simplify them
  - Very little differences in performances of the model based designs (Zohar & Chevret, JBS, 2008)
- “Translational Biostatistics:” Taking designs from the computer into the clinic.
Questions and Comments?

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