Clinical Trials – The New Frontier of Cancer Treatment

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The speaker has no financial or other conflicts of interest to disclose...

But I’ll keep trying...
“The charm of history and its enigmatic lesson consist in the fact that from age to age, nothing changes and yet everything is completely different.”

- Aldous Huxley
Discussion Topics

A Brief History of the Clinical Trial

Clinical Trials 101 – Key Concepts

Cancer Clinical Trials: Today’s Landscape

New Clinical Trial Designs
A Brief History of the Clinical Trial
A Brief History of the Clinical Trial

Babylon – 562 BC

King Nebuchadnezzar

- Role of diet in human health
- Meat-rich v. legume-restricted
- First trial to guide a public health decision

A Brief History of the Clinical Trial

Persia – 1025 AD

Avicenna – *Canon of Medicine*

Set forth rules for drug testing:

- Drug must be pure
- Use for a “simple disease”
- Test on at least 2 types of disease
- Quality of drug related to strength of disease
- Timing of observations should rule out natural healing
- Drug effect must be reproducible
- Animal trials should precede human

A Brief History of the Clinical Trial

Great Britain - 1747

James Lind – Father of the Clinical Trial

*Treatise on Scurvy* -1753

“They all in general had putrid gums, the spots and lassitude, with weakness of the knees.”

- Isolation
- Groups of 2
- Six therapeutic interventions
- Documentation
A Brief History of the Clinical Trial

1863 – United States

Austin Flint – *A Treatise on the Principles & Practice of Medicine*

First utilization of a placebo

“The favorable progress of cases was such as to secure for the remedy generally the entire confidence of the patients.”
A Brief History of the Clinical Trial

1946 – United Kingdom

Sir Austin Bradford Hill
Father of the Modern Clinical Trial

Streptomycin in Tuberculosis

- Meticulous trial design.
- Defined entry criteria and data collection.
- First widely publicized trial to incorporate randomization.
Clinical Trials 101 – Key Concepts
What is a Clinical Trial?

• Cancer clinical trials are research studies conducted by medical scientists to improve the care and treatment of cancer patients.

• Cancer clinical trials test ways to:
  – Diagnose and treat cancer in people
  – Prevent or reduce disease or treatment side effects
  – Prevent a recurrence of cancer
  – Improve the comfort and quality of life of people with cancer
  – Understand non-medical factors that impact outcomes for cancer patients
Drug Development

- Discovery of new drug in lab
- Drug tested in lab and animals
- FDA

- Food and Drug Administration approves Investigational New Drug (IND) application
- The drug can now be tested in humans through a clinical trial
Early Phase Clinical Trials

Phase 1 clinical trials
- What method of drug delivery and dosage is safest?
- How does the drug affect the human body?

Phase 2 clinical trials
- Does the drug have an effect on the cancer?
Late Phase Clinical Trials

**Phase 3 clinical trials**
- Is the new drug or combination of drugs better than the best current treatment?

Researchers submit New Drug Application (NDA) to FDA
- FDA decides whether to approve the drug for use in all patients
- Is it more effective or does it have fewer side effects than standard treatment?
Continued Study

FDA approves new drug for sale and marketing in the United States

New drug available by prescription for all patients who need it

Phase 4 clinical trials
- Ongoing research
- Study the effectiveness or side effects of an FDA-approved drug over time in a large population of patients
Traditional Clinical Trial Design

One Tumor Type, One Experimental Therapy, One Standard Therapy

Scenario 1

Experimental Drug → Tumor Type 1 → Randomization → Experimental therapy

Scenario 2

Experimental Drug → Target A → Randomization → Experimental therapy

Experimental Drug → Target A → Randomization → Standard therapy
Randomization

Randomization is the process of assigning clinical trial participants to treatment groups. Randomization gives each participant a known (usually equal) chance of being assigned to any of the groups. Successful randomization requires that group assignment cannot be predicted in advance.
Why Randomize?

If, at the end of a clinical trial, a difference in outcomes occurs between two treatment groups (say, intervention and control) possible explanations for this difference would include:

- the intervention exhibits a real effect;
- the outcome difference is solely due to chance;
- there is a systematic difference (or bias) between the groups due to factors other than the intervention.

Randomization aims to obviate the third possibility.
If I enter a clinical trial, there’s a good chance that I could receive a placebo

FALSE
Clinical Trials: Myths and Misconceptions

Clinical trials are the treatment of last resort

FALSE
If I enter a clinical trial, I’ll be treated like a “guinea pig”

FALSE
Clinical Trials: Myths and Misconceptions

Care and treatment received are free

TRUE & FALSE
Clinical Trials 101: Summary

Before making any treatment decisions, ask questions and gather information. The more information you have, the easier it will be to make decisions and manage challenges.

Potential benefits of participation in clinical trials

• Receive, at minimum, the best treatment available
• Be among the first to benefit from a new treatment
• Receive a lot of attention and support, including close monitoring to ensure safety
• Have access to doctors with extensive experience in the type of cancer you have
Cancer Clinical Trials: Today’s Landscape
The Cancer Landscape in 2015

• 1.65 million new cases predicted
• Almost 600,000 cancer related deaths
• 5 year survival rate has improved from 49% in the 1970’s to 68% from 2003-2009
• 14.5 million survivors compared with 3 million survivors in 1971
• Novel therapies becoming the norm – recent FDA approvals
  • Angiogenesis inhibitors – ramucirumab, sorafenib
  • Antibodies – obinutuzumab
  • Cell signaling inhibitors – dabrafenib, trametinib, idelalisib, ceritinib
  • Epigenome modifying agents - belinostat
A Revolution in Cancer Therapy

Genomics

Proteomics

Metabolomics

Immuno-oncology
The Promise of Precision Medicine

- Tumor traditionally classified by histology, tissue site
- Extract tumor biopsy
- Extract DNA from tumor to profile for somatic alterations
- Define “actionable” mutation profile of tumor
- Use genetic alteration profile to choose individualized targeted therapeutic

Problems with Current Trial Design

- Classical phase I, II, and III models require enormous resources
- Time to bring a new oncology drug to market 8-12 years
- Cost to bring a new drug to market can exceed $1 billion
- 70% of oncology drugs fail in phase II
- 59% of oncology drugs fail in phase III
- Have focused on histology-dependent strategies
- Limited collaboration between sponsors, academia, and funding sources
- Traditional models not designed to address “niche” agents with very small populations expected to benefit

Is There a Better Way?

Impact of biomarkers on clinical trial risk in breast cancer

Jayson L. Parker · Nadia Lushina · Prabhjot S. Bal · Teresa Petrella · Rebecca Dent · Gilberto Lopes

Biomarkers and Receptor Targeted Therapies Reduce Clinical Trial Risk in Non–Small-Cell Lung Cancer

Adam Falconi, BSc, Pharm, * Gilberto Lopes, MD, MBA, †‡ and Jayson L. Parker, PhD, MBA§

In advanced breast cancer between 1998-2012:

14% of drugs in development were approved
23% of drugs in development approved when selecting for Her2 status
Selecting for Her2 associated with a 27% reduction in costs

In advanced non-small cell lung cancer between 1998-2012:

Biomarker targeted therapy was associated with a six-fold increase in trial success

New Clinical Trial Designs
New Trial Designs

Methodologies

1. Biomarker guided design
   1. Basket trials
   2. Umbrella trials

2. Adaptive Design

Major Goals

1. Shorten time to get drugs to the patients who need them
2. Reduce costs
3. Increase the number of trial participants getting the best treatment
Basket Trials

One Molecular Abnormality Targeted Across Multiple Tumor Types

The Old Way - Three distinct trials

Driven by tumor type
Basket Trials

One Molecular Abnormality Targeted Across Multiple Tumor Types

Simultaneous execution of multiple studies

Experimental Drug -> Target A -> Tumor Type 1, Tumor Type 2, Tumor Type 3

NCI Molecular Analysis for Therapy Choice (NCI-MATCH)

**NCI MATCH SCHEMA**

1. **Genetic sequencing** → **Actionable mutation detected** → **Study agent** →
   - **Stable Disease, Complete or partial response (CR+PR)** → **Continue on study agent until progression** → **PD**
   - **Progressive disease (PD)** → **Check for additional actionable mutations**
     - **Yes** → **No additional actionable mutations, or withdraw consent** → **Off study**
     - **No** → **Off study**

1. CR, PR, SD, and PD as defined by RECIST
2. Rebiopsy; if additional mutations, offer new targeted therapy
NCI-MATCH – Distinctive Features

- Discovery Trial – to inform anticipated larger phase II/III studies
- Over 40 drugs pledged
- More than 15 pharmaceutical companies participating
- More than 20 single arm, phase II studies conducted in parallel
- Arms can be added or deleted without impacting other arms
Umbrella Studies

One tumor type, multiple molecular targets

Patients with a defined tumor type → Molecular characterization of biopsy → Target A, Target B, Target C

Arm A1, Arm A2, Arm B1, Arm B2, Arm C1, Arm C2

Histology & Target Driven

Basket/Umbrella Trials Summary

- A response to the explosion of potentially actionable mutations in human cancers.
- Resulting in an increase in public-private collaborations.
- Promise efficiency in drug evaluation compared with traditional histology-driven sequential studies.
- Appear optimally positioned to evaluate large effects of targeted agents on relatively rare targets.
- Can detect strong hints of activity in early phase studies if appropriately designed.
- Suggest of different types with shared molecular aberrations may be more similar than tumors from same type lacking molecular features.
- Most established in the Phase II setting with increasing exploration in Phase III.
Adaptive Trial Designs
Adaptive Trial Designs

Key Features

Planned modifications based on accumulating data within a study that does not undermine the validity or integrity of the study.

Trial Procedures:

Eligibility
Endpoints
Response Evaluation
Study Dose
Treatment Duration
Diagnostic Procedures

Statistical Procedures:

Randomization
Data Monitoring
Sample size
Statistical Analysis Plan

Adaptive Trial Designs

Key Features
1. All changes are pre-planned
2. Allows the trial to “learn” from early results
3. Can increase the proportion of patients getting the better treatment
4. May shorten the time it takes to complete the trial
5. Can be very complex to manage
Adaptive Trial Designs
Adaptive Randomization
Adaptive Trial Designs
Adaptive Randomization

Add certain type of balls into the urn according to the treatment response

Assign treatment according to the type of ball selected at random.
Adaptive Trial Designs in Action
Troxacitabine in Acute Myelogenous Leukemia

Adaptive Trial Designs in Action

Assign with higher probability to the better performing treatment

Randomize AML Patients

- Idarubicin + Cytarabine
- Troxacitabine
- Troxacitabine + Cytarabine

This arm dropped after 24\textsuperscript{th} patient

Trial stopped after 34 patients

Adaptive Trials in Action

Summary of Results – Complete Response by Day 50

Randomize AML Patients

- Idarubicin + Cytarabine
  - 10/18 = 56%

- Idarubicin + Troxacitabine
  - 3/11 = 27%

- Troxacitabine + Cytarabine
  - 0/11 = 0%
Strengths of Bayesian Adaptive Trials

- Potentially smaller trials
- Potentially shorter trials
- More accurate conclusions
- Able to address more questions
- Better treatment for patients in clinical trials
- Greatest potential in multi-armed trials
- Benefits limited but real in two-armed trials
- Suited to the task of pairing molecular signatures to targeted agents

The Promise of New Trial Design
Too good to be true?

PERSONALIZED MEDICINE | How redesigning a clinical trial can speed drug development

Traditional clinical trial
Takes essentially all patients with a disease being studied and is typically intended to eliminate differences in patient characteristics that could bias measures of drug effectiveness.

New trial design
Uses genetic profiles to highlight "biomarker" differences among patients and to match drugs to patients with biomarkers that predict a benefit.

PHASE II
Randomized or non-randomized trials: In a randomized trial, about 60 patients are put in two groups: One receives the experimental drug and the other serves as a control group. In a non-randomized trial, about 40 patients receive the experimental drug.

PHASE III
If a drug graduates to phase III, it typically takes 3,000 patients and about three years to determine if it is safe and effective enough for approval.

HISTORIC SUCCESS RATE
30% to 40%

PHASE III
Researchers expect that drugs graduating from phase 2 to phase 3 can be tested with 300 patients selected according to genetic profiles found to respond to the drug in phase II. It is hoped that this will shorten the time to approval.

PROBABILITY OF SUCCESS
85%

Source: Donald B. Berry, M.D., Anderson Cancer Center
Thank you.
If your doctor does not bring up clinical trials as a treatment option, don’t hesitate to ask.

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- [www.LLS.org/clinicaltrials](http://www.LLS.org/clinicaltrials), click on TrialCheck® search tool*
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  - Asks 11 simple questions about the patient
    - Questions include zip code, disease diagnosis and stage, treatment history and the patient’s age
    - Most questions are optional, but providing information allows TrialCheck to eliminate trials for which the patient is not eligible
  - Once the search is complete, clinical trials are organized by location, showing those closest to the patient first
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