Translational Statistics:
As Tool of Quality Control of Clinical Research
- Moving Beyond the Comfort Zone –
to Translational Statistics

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Outline

• Concept of Clinical Trial
• Role of Biostatistics
• Introduction of Classical p-value concept
  – From Classical Concept to New Concept
    • Translational Statistics
• Examples
• Challenges
What is a Clinical Trial?

Target Population

2\textsuperscript{nd} line for Brain tumor

Age : over 20 yrs
PS : 0 ~ 1

Randomization factors : PS, sex, tumor type, clinical site

Primary Endpoint : survival time

Secondary Endpoint : QOL

Sample Size : 222 (Trt A 110, Trt B 112)
Role of Biostatistics

Inference:

Point Estimate: Mean, Median, Confidence Interval

Hypothesis Test

Whether the treatment difference is real?
## Concept of Hypothesis Test

<table>
<thead>
<tr>
<th>Under null hypothesis</th>
<th>Truth (no one knows)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reject (Yes in efficacy)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Power</th>
<th>Type I error</th>
<th>Type II error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reject Yes efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do Not Reject</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Meaning of Hypothesis Test

• Only show probability under null hypothesis (no difference)

• **Does not** show any causal evidence
  – Q: Does smoking cause lung cancer?
    • Must be proved by basic science
ECMO STUDY (Comfort Zone)

- Neonatal extracorporeal membrane oxygenation (ECMO) Study
  - 1: Conventional: die: p = 0.95
  - 2: ECMO: survive: p = 0.95
  - 3: ECMO: survive: p = 0.7125 ran: Play-the-Winner
  - 4: ECMO: survive: p = 0.475
  - 5: ECMO: survive: p = 0.2968
  - 11: ECMO: survive: p = 0.01
  - 12: ECMO: survive: p = 0.006 Strong Controversy
• Statistical and ethical aspects

Medical decision-making
Classical Concept: Comfort Zone

One size fits all Concept

Classical Concept: Free Size Concept

Precision Medicine (Translational Stat.)

Selection of Target Population

Patient’s Choice
One Size Fits All: Classical Concept

Variety of background patients

• various races, different genes
• smoking, no smoking
• high blood pressure, low blood pressure
• high cholesterol, low cholesterol

One fits all concept: Do you believe that new treatment works for all patients?

Positive effect

Positive effect in subgroup

P < 0.05

Clinical Study

Negative effect

Negative effect in subgroup
One fits all concept: Do you believe that new treatment does not work for all patients?

Variety of background patients
- various races, different genes
- smoking, no smoking
- high blood pressure, low blood pressure
- high cholesterol, low cholesterol

P > 0.05

Positive effect in subgroup

Negative effect in subgroup

Clinical Investigation
One Size Fits All: Patient`s Selection (Irressa)

One fits all concept: Do you believe that new treatment does not work for all patients?

- various races, different genes
- smoking, no smoking
- high blood pressure, low blood pressure
- high cholesterol, low cholesterol

Variety of background patients

Positive effect

Asian, Female Adeno, Nonsmoker

Positive effect in subgroup

P > 0.05

Clinical Investigation

Negative effect

Negative effect in subgroup
Ex:

- **Irressa**
  - Japan, US: First surrogate marker, Response Rate was applied for approval, or conditional approval
  - FDA: Phase 3 placebo control trial is required?

- **Failed**
  - Subgroup analysis
    - Asian, Female, Non-smoker, Adeno.

- **Application of Surrogatemarker**
  - Pancreas Cancer
    - Survival is good enough for pts.
    - QOL can be another alternative endpoint
      - Pat`s choice
### Purpose
Improvements in Survival and Clinical Benefit with Gemcitabine as First-Line Therapy: A Randomized Trial: focus on disease related response

### Target Population
Advanced Pancreas Cancer

### Endpoints
- **Primary endpoint**: CBR (Clinical Benefit Response)
- **Secondary Endpoint**: Response Rate, Survival, Time to Progression

### Eligibility Criteria
1. Baseline KPS 80
2. Baseline analgesic consumption 10 mg/d (morphine equivalent mg/d)
3. Baseline pain intensity score 20 mm
Eligible only if one or more of the above conditions are met

### TRT
- Gemcitabine (63) 、5-FU (63)

### Result
1. **CBR rate**: Gem 23.8% (15/63) vs 5-FU 4.8% (3/63)  
   \( p = 0.0022 \)
2. **MST**: Gem 5.7 month vs 5-FU 4.4 month  
   \( p = 0.0025 \)
3. **median TTP**: Gem 2.3 month vs 5-FU 0.9 month  
   \( p = 0.0002 \)
4. **Response Rate**: Gem 5.4% vs 5-FU 0%
Primary criteria: Pain Intensity (pain level, Analgesic dose) and KPS.
Secondary criteria: weight gain are composed in Clinical Benefit Response

For each variable
Positive case
Stable case
Negative case
Are determined
Example: PEACE Trial (Braunwald et al., 2004) (Comfort Zone)

Angiotensin-Converting–Enzyme Inhibition in Stable Coronary Artery Disease

The PEACE Trial Investigators
A cardiovascular clinical trial on patients who survived a recent Myocardial Infarction.

—Comparison of ACEi versus placebo in addition to standard therapy.

Double-blind, 8290 patients were randomly assigned to receive either ACEi (4158 pts) or matching placebo (4132 pts).

The median follow-up time was 4.8 years and the longest was over 7 years.
PEACE Trial: Survival (ACEi vs Placebo)
• In papreserved left ventricular function who are receiving “current standard” therapy and in tients with stable coronary heart disease and whom the rate of cardiovascular events is lower than in previous trials of ACE inhibitors in patients with vascular disease, there is no evidence that the addition of an ACE inhibitor provides further benefit in terms of death from cardiovascular causes, myocardial infarction, or coronary revascularization.
Continuation: Follow up publication

(Translational Statistics)

Coronary Heart Disease

Renal Function and Effectiveness of Angiotensin-Converting Enzyme Inhibitor Therapy in Patients With Chronic Stable Coronary Disease in the Prevention of Events with ACE inhibition (PEACE) Trial

Scott D. Solomon, MD; Madeline M. Rice, PhD; Kathleen A. Jablonski, PhD; Powell Jose, BS; Michael Domanski, MD; Marc Sabatine, MD; Bernard J. Gersh, MD, ChB, DPhil; Jean Rouleau, MD; Marc A. Pfeffer, MD, PhD; Eugene Braunwald, MD; for the Prevention of Events with ACE inhibition (PEACE) Investigators
Subgroup analysis on renal function
**S-CUBE: Study design**

**Sorafenib-refractory advanced HCC**

- **Main Inclusion criteria:**
  - Confirmed diagnosis of HCC
  - Age 20 years and older
  - Ineligible for surgical or local-regional therapy
  - Child-Pugh score 5-7
  - ECOG PS 0-1
  - At least one target lesion

- **Criteria for refractory to Sorafenib treatment:**
  1. Disease progression with sorafenib therapy.
  2. Discontinuation of sorafenib due to an AE

**Randomize**

**S-1 (N=223)**
40-60 mg b.i.d d1-28 of a 42-day

**Placebo (N=111)**

**Primary endpoint:** Overall survival

**Efficacy analysis:** Full analysis set (S-1 group: 222 pts, Placebo group: 111 pts.)

**Stratification factors:**
1. Medical institutions
2. Extrahepatic metastasis and/or vascular invasion (yes vs. no)

S-CUBE was a randomized, double-blind, phase III trial evaluating the efficacy and safety of S-1 in patients with sorafenib-refractory advanced hepatocellular carcinoma.

**Overall survival**

- Events (Censorns): S-1: 183 (39), Placebo: 100 (11)
- MST S-1: 337.5 days, Placebo: 340.0 days
- Logrank p=0.2201
  - HR=0.86, 95% CI [0.67, 1.10]

**Forest plot of hazard ratio for OS**

Although S-1 did not significantly improve overall survival in all cohort, the subgroup analysis of the heterogeneous population with advanced HCC showed the efficacy of S-1 on OS was different depending on patient characteristics.
Final step: Identification of enrichable (non-enrichable) subgroup

- KM curves of the enrichable (non-enrichable) subgroup $q_0 = 0.70$ as the threshold value.
- This means 70% of the total population was identified as enrichable population.
Translational Statistics

Identification of a high-response patient population

High-response patient population

- Events (Censors) S-1: 113 (32), Placebo: 69 (5)
- MST S-1: 426.0 days, Placebo: 375.5 days

Logrank p=0.0156
HR=0.69, 95%CI [0.51, 0.93]

- High-response patients are classified as those with the following criteria; (219 patients; 65.8% of the total)

1) TNM stage III, IVa or IVb
2) Child-Pugh class A
3) Levels of both the tumor markers are not high
   - AFP <400 ng/mL
   - or
   - AFP ≥400 ng/mL and PIVKA-II <10000 mAU/mL

- The median OS of S-1 group was significantly longer than that of placebo group
Trend of Statistical Analysis Approach: Moving from the Comfort Zone

• Regenerative Medicine
  – Small # of Pts: Small Sample size
  – Heterogeneity of Pts’ Background: Large Variability of Data
  – Previous Clinical Trial Data: Not available
  – Placebo control is required?
    • Natural Disease Course model from Epi. Data
  – New Endpoint will be required?
    • Not from statistical view point, but from Clinical and patient’s view
      – Clinical Benefit Response Variable (CBR) in Pancreas Cancer

• Patient’s Selection
  – President Obama in US
    • Precision Medicine Initiative
    • US FDA Guideline
Summary

• Move out from Classical Approach (P-value concept)
  – From p-value to estimation of efficacy

• Similar to regenerative medicine
  – From hypothesis test to estimation
  – Selected target population
    »Enrichment analyses

• New Innovative Approach
  – Medical big data such as Epi. Study is essential
  – Thorough Discussion among MD and Stat is essential
Thank you very much for your attention