Phase I Trials

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Learning Objectives

- Understand the purpose of phase I trials
- Become familiar with concepts of dose limiting toxicities (DLTs), recommended phase II dose (RPTD), and optimal biological dose (OBD)
- Provide an overview of the types of trial designs used to determine the RPTD
- Introduction to the role of biomarkers in phase I trials
Definitions of Phase I Trial

First evaluation of a new cancer therapy in humans

- First-in-human, first-in-class single agent
- First-in-human, non first-in-class single agent
- Combination of novel agents
- Combination novel agent and approved agent
- Combination of approved agents
- Combination of novel agent and radiation therapy

Eligible patients usually have refractory solid tumors of any type
Prerequisites for Phase I

• Unmet clinical need
• Biological plausibility (target validation)
• Expectation of benefit (preclinical activity)
• Reasonable expectation of safety (preclinical toxicology)
• Basis for selection of starting dose
Objectives of Phase I Trial

- **Primary objective:**
  - Identify dose-limiting toxicities (DLTs) and the recommended phase II dose (RPTD)

- **Secondary objectives:**
  - Describe the toxicity profile of the new therapy in the schedule under evaluation
  - Assess pharmacokinetics (PK)
  - Assess pharmacodynamic effects (PD) in tumor and/or surrogate tissues
  - Document any preliminary evidence of objective anti-tumor activity
Key Concepts: DLT

- **Dose-limiting toxicity (DLT):**
  - Toxicity that is considered unacceptable (due to severity and/or irreversibility) and limits further dose escalation
  - Specified using standardized grading criteria, e.g. Common Terminology Criteria for Adverse Event (CTCAE)
  - DLT is defined in advance prior to beginning the trial and is protocol-specific
  - Typically defined based on toxicity seen in the first cycle
CTCAE Criteria

• Grade 1 = MILD
• Grade 2 = MODERATE
• Grade 3 = SEVERE
• Grade 4 = LIFE-THREATENING
• Grade 5 = FATAL
Generally can tolerate higher degrees of toxicity because the interval between treatments allows for rest and recovery

- Examples:
  - Grade 3 or worse non-hematologic toxicity despite supportive measures
  - ANC < 0.5 x 10^9/L for ≥ 5 or 7 days
  - Febrile neutropenia (ANC < 1 x 10^9/L, fever ≥ 38.5°C)
  - Platelets < 25 x 10^9/L or thrombocytopenic bleeding
  - Inability to re-treat patient within 2 weeks of scheduled treatment
DLT Definitions – Daily dosing

Threshold for DLTs is lower

- Some Grade 2 toxicities may be unacceptable and intolerable due to their persistence and lack of time period for recovery

- Examples:
  - Grade 2 intolerable or worse non-hematologic toxicity despite supportive measures
  - Recurrent Grade 2 intolerable toxicity after interruption
  - Grade 3 or worse hematologic toxicity
  - Inability to complete a pre-specified percentage of treatment during the cycle due to toxicity (e.g. missing 20-25% of doses)
Terms maximum administered dose (MAD), maximum tolerated dose (MTD) are confusing

Better Term = Recommended phase II dose (RPTD):
- Dose associated with DLT in a pre-specified proportion of patients (e.g. < 33%) – dose that will be used in subsequent phase II trials
Key Principles of Phase I Trials

• Start with a safe starting dose

• Minimize # of pts treated at sub-toxic doses

• Escalate dose rapidly in the absence of toxicity

• Escalate dose slowly in the presence of toxicity

• Expand patient cohort at RPTD
Patient Population

- “Conventional” eligibility criteria- examples:
  - Advanced solid tumors unresponsive to standard therapies or for which there is no known effective treatment
  - Performance status (e.g. ECOG 0 or 1)
  - Adequate organ functions (e.g. ANC, platelets, Creatinine, AST/ALT, bilirubin)
  - Specification about prior therapy allowed
  - Specification about time interval between prior therapy and initiation of study treatment
  - No serious uncontrolled medical disorder or active infection
Patient Population

“Agent-specific” eligibility criteria- examples:

- Specific organ exclusions:
  - Cardiac function (e.g. QTc ≥450-470 ms, LVEF ≤ 50%, etc), acute MI/CVA if preclinical data or prior clinical data of similar agents suggest cardiac risks
  - Recent hemorrhage or ongoing anticoagulation for agents with bleeding risk (ie. antiangiogenic)
  - Diabetes or fasting plasma hyperglycemia ≥ 7.9 mmol/L for agents with risk of hyperglycemia (ie. PI3K/mTOR, IGF-1R)
- Prohibited medications if significant risk of interaction with study drug
- Prior exposure to drug in same class
Pre-clinical Toxicology

- Typically a rodent (mouse or rat) and non-rodent (dog or non-human primate) species

- Reality of animal organ specific toxicities – very few predict for human toxicity
  - Myelosuppression and gastrointestinal toxicity more predictable
  - Hepatic and renal toxicities – large false positive

- Typical starting dose:
  - $1/10^{th}$ of LD10 rodents = lethal dose in 10% of animal
  - OR
  - $1/3^{rd}$ of TDL large animals = lowest dose that causes any toxicity in animals
<table>
<thead>
<tr>
<th>Species</th>
<th>To convert animal dose in mg/kg to dose in mg/m², multiply by Km below:</th>
<th>To convert animal dose in mg/kg to HED in mg/kg, either:</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Divide animal dose by</td>
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<tr>
<td>Human</td>
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<td>–</td>
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<tr>
<td>Child (20 kg)</td>
<td></td>
<td>–</td>
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<tr>
<td>Mouse</td>
<td>3</td>
<td>12.3</td>
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<tr>
<td>Hamster</td>
<td>5</td>
<td>7.4</td>
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<tr>
<td>Rat</td>
<td>6</td>
<td>6.2</td>
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<tr>
<td>Ferret</td>
<td>7</td>
<td>5.3</td>
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<tr>
<td>Guinea pig</td>
<td>8</td>
<td>4.6</td>
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<tr>
<td>Rabbit</td>
<td>12</td>
<td>3.1</td>
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<tr>
<td>Dog</td>
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<td>Primates:</td>
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<tr>
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<tr>
<td>Marmoset</td>
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<tr>
<td>Micro-pig</td>
<td>27</td>
<td>1.4</td>
</tr>
<tr>
<td>Mini-pig</td>
<td>35</td>
<td>1.1</td>
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</table>
Principles of Dose Escalation

• The higher the dose, the greater the likelihood of efficacy
  – Dose-related acute toxicity is regarded as a surrogate for efficacy
  – The highest safe dose is the dose most likely to be efficacious
  – This dose-effect assumption is primarily for cytotoxic agents and may not apply to molecularly targeted agents
Typically intrapatient dose escalation is not allowed
# Classical 3+3 Design

<table>
<thead>
<tr>
<th># of pts w/DLT</th>
<th>Action</th>
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<tbody>
<tr>
<td>0/3</td>
<td>Increase to next level</td>
</tr>
<tr>
<td>1/3</td>
<td>Accrue 3 more pts at same dose level</td>
</tr>
<tr>
<td>1/3 + 0/3</td>
<td>Increase to next dose level</td>
</tr>
<tr>
<td>1/3 + 1/3</td>
<td>Stop: recommend previous dose level</td>
</tr>
<tr>
<td>1/3 + 2/3</td>
<td>Stop: recommend previous dose level</td>
</tr>
<tr>
<td>1/3 + 3/3</td>
<td>Stop: recommend previous dose level</td>
</tr>
<tr>
<td>2/3</td>
<td>Stop: recommend previous dose level</td>
</tr>
<tr>
<td>3/3</td>
<td>Stop: recommend previous dose level</td>
</tr>
</tbody>
</table>
**Modified Fibonacci Dose Escalation**

- Attributed to a merchant from the 13th century
- Doses increase by: 100%, 66%, 50%, 40%, 33%, etc.
- Standard “3+3” design: 3 patients per cohort, escalating to 6 if DLT occurs
- Dose escalate until DLT observed and MTD/RPTD defined
- **Advantages:**
  - relatively safe, straightforward, clinician-friendly
- **Disadvantages:**
  - lacks statistical foundation and precision, potentially treating a large proportion of patients at sub-therapeutic doses, time consuming
Limitations of 3+3 Design

- Many patients treated at ineffective doses in initial cohorts
- Escalation to RPTD can take a long time
- High risk of severe toxicity in late cohorts
- Wide confidence intervals for RPTD
Accelerated Titration Design (Rule-Based)

- First proposed by Simon et al (J Natl Cancer Inst 1997)
- Several variations exist:
  - usual is doubling dose in single-patient cohorts till Grade 2 toxicity
  - then revert to standard 3+3 design using a 40% dose escalation
  - intrapatient dose escalation allowed in some variations
  - More rapid initial escalation
Classical 3+3 Design

- Dose
  - 1 pt
  - 3 pts
  - RPTD
  - 3 pts

- Grade 2 Toxicity
  - 1 pt

- MAD
  - 3 pts
  - +
  - 3 pts

- DLT
  - 3 pts
  - +
  - 3 pts

- DLT
  - 3 pts

- RPTD
  - 3 pts
Modified Continual Reassessment Method (mCRM)

- Bayesian method
- Pre-study probabilities based on preclinical or clinical data of similar agents
- At each dose level, add clinical data to better estimate the probability of RPTD being reached
- Fixed dose levels for escalation
- **Advantages** – more pts treated at therapeutic levels, more dose levels explored
- **Disadvantages** – requires biostatistician, does not save time
Dose Escalation with Overdose Control (EWOC)

- Bayesian method

- After each cohort of patients, the posterior distribution is updated with DLT data to obtain $\pi_d$ (probability of DLT at dose $d$). The recommended dose is the one with the highest posterior probability of DLT in the “ideal dosing” category.

- The overdose control mandates that any dose that has > 25% chance of being in the “over-dosing” or “excessive over-dosing” categories, or > 5% chance of being in the “excess-overdosing” category, is not considered for dosing.
Example of EWOC Design

- **Ideal Dosing**: This bar should be the highest percentage.
- **Under-Dosing**: This % should be minimal.
- **Over-Dosing**: This bar should be below 25%.
- **Excessive Over-Dosing**: This bar should be 0%.

### Drug at 0.5mg
- 7%: 44%
- 60%: 52%
- 30%: 4%
- 3%: 0%

### Drug at 0.75 mg
- 7%: 7%
- 60%: 66%
- 30%: 27%
- 3%: 0%

### Drug at 1.0 mg
- 7%: 0%
- 60%: 35%
- 30%: 64%
- 3%: 0%
A 3+3 design

B PK guided escalation

C Accelerated titration

D Up-and-down

E mCRM

F EWOC

Le Tourneau, Lee, Siu, JNCI
Pharmacokinetic (PK) Assessment

• “What the body does to the drug”
  • Absorption, distribution, metabolism, and excretion
• PK parameters – provide information about the drug and/or its metabolites
  • Cmax (peak concentration)
  • AUC (exposure)
  • T_{1/2} (half-life)
  • Clearance (elimination)
• Requires serial sampling to characterize fully
  • ie. Pre-dose, 30m, 1h, 2h, 4h, 6h, 8h, 24h
  • Cycle 1 Day 1 and repeat when drug is expected to have reached steady state serum concentrations
PK: Time x Concentration Plot

Serum concentration (mg/mL)

AUC

Time (hours)
Challenges of Molecularly Targeted Agents (MTAs)

- General requirement for long-term administration: *pharmacology and formulation critical*

- Difficulty in determining the optimal dose in phase I: *MTD versus Optimal Biological Dose (OBD)*

- Absent or low-level tumor regression as single agents: *problematic for making go no-go decisions*

- Need for large randomized trials to definitively assess clinical benefit: *need to maximize chance of success in phase III*
Key Concepts

• Optimal biological dose (OBD):
  – Dose associated with a pre-specified desired effect on a biomarker

  – Examples:
    • Dose at which $\geq XX\%$ of patients have inhibition of a key target in tumor/surrogate tissues
    • Dose at which $\geq XX\%$ of patients achieve a pre-specified immunologic parameter

  – Challenge with defining OBD is that the “desired effect on a biomarker” is generally not known or validated before initiation of the phase I trial
Definition of a Biomarker

- “A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacological responses to a therapeutic intervention”
  » NIH Working Group, 2011

- “A molecular, cellular, tissue, or process-based alteration that provides indication of current, or more importantly, future behavior of a cancer.”
  » Hayes et al JNCI, 1996
Biomarkers in Phase I Trials

- Based on pre-clinical studies
  - Pharmacokinetics
  - Proof-of-mechanism
  - Establish optimal biological dose in some trials (especially if little or no toxicity expected)
- Molecular enrichment
  - Proof-of-concept – anti-tumor activity
Pharmacodynamic Biomarkers (PD)

• “What the drug does to the body (or tumor)”
  • Provide therapeutic information about the effect of a therapeutic intervention on the patient and/or tumor
• Tumor PD biomarkers
  – Phosphoprotein (IHC)
  – Gene expression (RT-PCR, microarray)
  – Cell surface markers (Flow cytometry)
  – Functional imaging
    – FDG-PET, FLT-PET, DCE MRI, etc
• Surrogate Normal Tissue PD biomarkers
  • Hair follicles
  • Skin biopsies
  • Peripheral blood mononuclear cells (PBMCs)
Pharmacodynamic Endpoints

- Phase I PD biomarkers
  - Requires assessment before and during treatment
  - Should be correlated with PK parameters
  - Proof of mechanism
    - Is a new drug hitting its target?
  - Establish optimal biological dose
    - Especially if little of no toxicity expected (monoclonal antibodies)
  - Often more practical to perform in expansion cohort at recommended phase II dose
Changing Paradigm of Biomarker-Guided Early Drug Development

Abundance of drug discovery

Scarcity of drug discovery

Pre-Clinical Development

Phase I

Biomarker – Proof of mechanism (Pharmacodynamic Biomarkers)

Phase II

Phase II-III – Proof of principle (Predictive Biomarkers)

Commercialization

Adapted from Eli Lilly and Company
Expansion Cohorts in Phase I Trials

- Limited # of pts (N=6-12) treated at MTD after dose escalation
- Confirm safety and tolerability of MTD = RPTD
- Increasing use over time
- Expansion cohort ≠ properly conducted phase II

Figure 1. Use of Expansion Cohorts in Phase I Trials

Manji A et al JCO 2013 (in press)
Enrichment Strategies for Phase I

- Early testing of a new drug in enriched population can accelerate development of new drug

- Lack of activity in biomarker +ve subpopulation treated at MTD may lead to “No GO” signal to halt development
Challenges of Enrichment Approach

• Screening for rare alterations
  • Sequential biomarker testing is inefficient
  • Patients who have exhausted standard treatment do not have time to wait for biomarker screening
• Many large academic institutions have started molecular profiling programs for matching patients to trial based on genotype
  • Testing and interpretation is complex
  • Not funded by public health care systems
  • Requires large portfolio of trials for matching
  • Tumor heterogeneity is problematic
Phase I Trials Risk/Benefit Ratio

- Response Rate 4-6% (first in human)
- Higher for combination studies involved approved drug (~15%)
- Majority of responses occur at 75-125% of recommended phase II dose
- Response is a surrogate endpoint
  - Direct patient benefit is difficult to measure
- Risk of toxic death is low (<0.5%)
Pitfalls of Phase I Trials

- Maximum tolerated dose may not be appropriate for molecularly targeted agents
- Chronic toxicities usually cannot be assessed
- Cumulative toxicities usually cannot be identified
- Uncommon toxicities will be missed
# Phase I Trials and Infrequent Toxicities

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Probability of NOT observing a serious toxicity occurring at a rate of:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>1</td>
<td>0.90</td>
<td>0.80</td>
</tr>
<tr>
<td>2</td>
<td>0.81</td>
<td>0.64</td>
</tr>
<tr>
<td>3</td>
<td>0.73</td>
<td>0.51</td>
</tr>
<tr>
<td>6</td>
<td>0.53</td>
<td>0.26</td>
</tr>
<tr>
<td>10</td>
<td>0.35</td>
<td>0.11</td>
</tr>
<tr>
<td>15</td>
<td>0.21</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Summary

• Phase I trials are critical for the evaluation of new therapies – translation from the lab to the clinic

• Patient safety/well-being is the most important principle in phase I

• Most drugs follow the MTD/RPTD paradigm

• Biomarker studies are essential to evaluate new cancer drugs

• Phase I trials are increasingly complex and require good team science