Optimizing Dosing of Oncology Drugs
Optimizing Dosing of Oncology Drugs

Richard L. Schilsky, M.D.
American Society of Clinical Oncology
Current Approach to Dose Determination in Oncology

- Aimed at the “maximum-tolerated dose” (MTD) to increase chance of obtaining an efficacy signal
- MTD is identified in phase 1 trials, often in heavily pre-treated patients
- MTD may be the only dose evaluated in phase 2 and phase 3 trials
- Clinical trials define a tolerable dose for a population, and adjusting dose for individual patients is done empirically
Traditional Approach to Dose Finding

Determination of dose for registration-directed studies

Phase I ± Phase II

Registration-directed Studies (‘R-Studies’)

Limited learning about variability of drug exposure

Commercial Access

Requirement for post-marketing commitments including exposure-response analyses

*simplified for the purpose of illustration
Limitations of the Current Approach

- Dose (exposure)-response relationships are rarely well defined
- High rate of dose reductions in some clinical trials, recent examples in briefing document
- Failure to identify patients who may benefit from higher dose/exposure
- For some targeted agents, the “optimal biologic dose” may be that which results in saturation of a drug target, rather than the MTD
- Does not adequately evaluate late onset or cumulative toxicities or changes in tolerability over time
Many Factors Lead to Variable Drug Responses

• Genetic polymorphisms in drug transporters or drug-metabolizing enzymes
• Concomitant medications
• Age, body weight, hepatic and renal function
• Comorbidities
• “Food effect” on absorption of oral drugs
• Therefore, any dose chosen will be too high for some patients, too low for others.
Charge to the Panel

• Discuss **what** data needs to be collected to optimize dosing
• Discuss **how** this data can be used to optimize dosing
• Discuss **when** this data should be collected
Proposed Path

- **Phase 1:** Define a dose for future studies; preliminary characterization of pharmacokinetics (PK), include pharmacodynamic endpoints (PD) to assess target inhibition if possible.
- **Phase 2:** Define drug activity and include exploration of dose variations, continued PK and PD measurements.
- **Phase 3:** Incorporate population PK data to understand relationships between drug exposure and key clinical outcomes.
- When subjective toxicities are identified, use validated tools (if available) to assess patient-reported outcomes (PROs).
- **Post-market:** Use data collected in phase 1-3 to modify doses based on observed exposure, efficacy and tolerability.
How can this approach improve clinical outcomes?

- Definition of the ranges of toxic and therapeutic drug concentrations may, in some cases, enable monitoring of patient drug levels. This could be used to guide treatment decisions and may be particularly valuable for chronic treatment.

- Collection of drug exposure and clinical outcome data (i.e., tolerability, adverse events, efficacy) in the post-market setting could improve understanding of “real-world” patient experience with a drug and vulnerable populations.
When should dose exploration be performed?

• Premarket (ideally, phase 2): Phase 2 dose exploration could inform dose selection for phase 3:
  • Less likely to choose a dose too high and observe excessive toxicity
  • Less likely to choose a dose too low and observe inadequate efficacy

• Challenges:
  • May slow the development of potentially important new drugs
  • May be excessively burdensome when there is uncertainty whether the drug will ultimately be approved
  • May be difficult to assess pharmacodynamic endpoints if drug target not well understood
When should dose exploration be performed?

• Post-market dose-exploration may be used to refine recommended dose when premarket dose exploration is unfeasible, but also poses challenges:
  • Patients may not want to participate in a trial of drug already on the market
  • Difficult to perform these studies in a timely manner
• Potential opportunity in the window of time between the completion of registration trials and marketing approval.
Speakers

- **Atiqur Rahman, Ph.D.**, Division of Clinical Pharmacology V, FDA
- **Daniel Auclair, Ph.D.**, Multiple Myeloma Research Foundation
- **Lori Minasian, M.D.**, National Cancer Institute
- **Oliver Rosen, M.D.**, Millennium: The Takeda Oncology Company
- **Richard Pazdur, M.D.**, Office of Hematology and Oncology Products, FDA
Optimizing Dosing of Oncology Drugs

Atiqur Rahman, Ph.D.
Office of Clinical Pharmacology, FDA
Problem

• MTD based dose may not be appropriate for targeted therapy

• Dose selection based on MTD causing serious toxicities in phase 1b/2/3 and in post-marketing trials

• Doses used in Phase 2 and 3 often achieve concentrations that may substantially surpass concentrations needed to inhibit or stimulate the intended target (s)
  – not sufficiently specific to only hit the mechanistic/biologic target alone
  – off-target inhibition→toxicity?
Dose-Exposure Relationship

• Why is understanding exposure (PK/PD) important for dose optimization?

• How can exposure (PK/PD) help in optimizing the dose in drug development?
Exposure Effect Relationship

Influence of intrinsic and extrinsic factors on drug levels and therapeutic effects

- **Dose** → **Exposure** → **Target** → **Effect**

Concentration, µg/ml

<table>
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<tr>
<th>Concentration, µg/ml</th>
<th>Ther. level</th>
<th>Food: 2x↑</th>
<th>DDI: 8x↑</th>
<th>Organ Dys 4x↑</th>
<th>DDI: 5x↓</th>
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<tbody>
<tr>
<td>0</td>
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<td>400</td>
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<td>800</td>
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</table>

**Effect**

**Toxicity**

**Efficacy**
How can PK/PD help in optimizing dose in drug development?
Integration of Information
Target inhibition, PK and PD

% of BCR ABL Mutants recovered in the presence of a drug

Phase 1/2 PD Data: Biomarker of Activity

Dose Cohort
Number of Patients
< 25%
25 to 50%
> 50%

Dose (mg)
Mean(SE) Concentration (nM)
Cmax
Cmin

Frequency of recovered clones (%)

Mean(SE) Concentration (nM)
Cmax
Cmin

% of BCR ABL Mutants recovered in the presence of a drug
Path Forward

• Early Drug development
  – Identify targets
  – Identify optimal concentrations (IC$_{50}$, IC$_{90}$) for target effects
  – Determine correlation of human PK to
    • in vivo biomarker
    • in vitro target concentrations

• Phase 2 Development
  – Adaptive design to explore more than one dose
    • Optimal biologic dose
    • Near MTD dose
    • Collect PK and evaluate exposure activity and safety relationships

• Phase 3 Development
  – Sparse PK samples in all patients
    • Evaluate relationships between covariates influencing exposure and key clinical outcome (including biomarkers)
    • Develop rationale for dose escalation or reduction for approval and labeling

• Post-Marketing Trials
  – Refine dose if not optimized during development (difficult to do)
  – Sparse PK sampling in all patients
    • Evaluate relationships between exposure and long term toxicity
Carfilzomib PX-171-003 Studies

Study Population
- Progressive disease required at study entry
- Relapsed after ≥2 prior lines of therapy
  - Must include BTZ
  - Must include THAL or LEN
- Refractory to last regimen

003-A01
(N=46)
- Carfilzomib
  - 20 mg/m² IV
  - QD x 2 for 3 weeks (28-day cycle)

003-A1
(N=266)
- Carfilzomib
  - Dose escalation to 27 mg/m² after 1st cycle
  - (maximum of 12 cycles)

Jagannath et al. ASH 2009; Siegel et al. Blood 2012
Carfilzomib Dosing Schedule & PD

QDx2, weekly for 3 weeks (28 day cycle)

% proteasome inhibition

Time (weeks): 1 2 3 4

CD138+ (Bone Marrow) | Blood | PBMC
---|---|---
LLVY | CT-L | CT-L | CT-L
ProCISE | Beta5 | Beta5 | LMP7
| LMP7 | Beta2 | LMP2
| MECL1 | Beta1 | MECL1
# Patients Analyzed | 40 | 74 | 71

Lee et al., ESMO-TAT Meeting 2011
Carfilzomib EAP

- Single arm study in relapse refractory patients
- Same 20 -> 27 mg/m² design as PX-171-003-A1
- Almost 350 patients enrolled over an 11 months period
Higher doses Carfilzomib PD

Lee et al., ESMO-TAT Meeting 2011
Relating Clinical Outcomes in Multiple Myeloma to Personal Assessment of Genetic Profile

Basic Trial Information

<table>
<thead>
<tr>
<th>Phase</th>
<th>Type</th>
<th>Status</th>
<th>Age</th>
<th>Sponsor</th>
<th>Protocol IDs</th>
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<tr>
<td>No phase specified</td>
<td>Biomarker/Laboratory analysis, Natural history/Epidemiology, Supportive care</td>
<td>Active</td>
<td>18 and over</td>
<td>Other</td>
<td>MMRF-11-001 NCT01454297</td>
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CoMMPass Grade 3-4 AEs versus PROs/QoL
MMRF Gateways

https://research.themmrf.org

https://community.themmrf.org
Subjective Toxicities & (PRO-CTCAE) Patient Reported Outcomes version of CTCAE

Lori Minasian, M.D.
National Cancer Institute
Adverse Event Reporting

• Clinicians Trained to Recognize Serious Effects
  • Accurately Capture SAEs
  • Clinicians Tend to Under-report Bothersome Effects

• Patients’ Report of Side Effects Correlates Better with Function and Overall Health Status
  • May Better Reflect Tolerability over Time
  • Chronic Bothersome Side Effects May Reduce Adherence

• Optimal to Capture Both in Integrated Fashion
Clinician & Patient Reports are Discrepant

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patient graded higher</th>
<th>Agreement</th>
<th>Clinician graded higher</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>7%</td>
<td>34%</td>
<td>41%</td>
</tr>
<tr>
<td>Pain</td>
<td>7%</td>
<td>19%</td>
<td>60%</td>
</tr>
<tr>
<td>Constipation</td>
<td>3%</td>
<td>24%</td>
<td>69%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11%</td>
<td></td>
<td>85%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10%</td>
<td>18%</td>
<td>66%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
<td>14%</td>
<td>77%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6%</td>
<td>26%</td>
<td>52%</td>
</tr>
<tr>
<td>Cough</td>
<td>4%</td>
<td>18%</td>
<td>67%</td>
</tr>
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</table>

- Grade difference of 2
- Grade difference of 1
- Agreement
- * ≤ 2 percent

Baseline, Lancet Oncol, 2006
# PRO-CTCAE Measurement System

## 1. Symptom Library
- 78 symptomatic adverse events drawn from CTCAE
- PRO-CTCAE questions evaluate symptom occurrence, frequency, severity, and interference

## 2. System for Survey Administration
- Web-based system to customize surveys and manage survey administration
- Patient responds to surveys using web, tablet or interactive voice response (IVRS) telephone system
- Conditional branching (skip patterns)
- Write-ins with automatic mapping to standardized terminology

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### Images
- Patient using a tablet
- Doctor using a computer
- Medical professional monitoring a device
CTCAE vs. PRO-CTCAE Item Structures

### CTCAE

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tr>
<td>Mucositis oral</td>
<td>1</td>
<td>Asymptomatic or mild symptoms; intervention not indicated</td>
<td>Moderate pain; not interfering with oral intake; modified diet indicated</td>
<td>Severe pain; interfering with oral intake</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>-</td>
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### PRO-CTCAE

Please think back over the past 7 days:

What was the **severity** of your MOUTH OR THROAT SORES at their WORST?
None / Mild / Moderate / Severe / Very severe

How much did MOUTH OR THROAT SORES **interfere** with your usual or daily activities?
Not at all / A little bit / Somewhat / Quite a bit / Very much
Current Status & Ongoing Activities

• Standard Analytic Validation for Patient Reported Outcome Measure Nearly Completed
  – Reliability, Validity, Mode Equivalence, Group Differences
  – PRO-CTCAE Can Be Used For Descriptive Information

• Understanding Clinical Validity, Interpretation, & Clinical Utility is Evolving
  – Incorporation of PRO-CTCAE Scores into Clinician Grading
  – Integration of Information into Study Conduct
  – Use in Analyzing Tolerability
Potential Utility of PRO-CTCAE

- **Phase I:** Exploratory
  - Gauge side effects relative to dose escalation; refine measurement approaches (items, timing) for later phase studies

- **Phase II:** Describe Toxicity in Depth
  - Assess tolerability of the recommended phase II dosing
  - Identify chronic symptomatic toxicities that may impair adherence
  - Explore approaches (schedule/dosing, supportive care) to reduce symptomatic adverse effects

- **Phase III:** Assess Overall Benefit/Risk for Regimen
  - Evaluate efficacy and tolerability on a wider scale
  - Assess impact of dosing modifications to reduce chronic symptomatic toxicities on overall benefit/risk

- **Phase IV:** Efficacy → Effectiveness
  - Optimize tolerability
  - Tailor regimens for vulnerable sub-populations (comorbidities, frail, older adults)
Phase 2 B Comparative Tolerability

- Two oral agents with comparable efficacy and clinician-rated toxicity in Phase II trials
  - Research Question: Are there subtle tolerability differences between the two agents that might become important in Phase III and which can be detected with inclusion of PROs in Phase II?
- Randomized phase II study with efficacy and patient-reported tolerability as the primary endpoints

Randomize

Agent A

Agent B

Endpoints
  - Efficacy
  - Patient-Reported Tolerability (PRO-CTCAE)
Tolerability of Maintenance Therapy

Research Question:
What is the chronic tolerability of bortezomib maintenance therapy in multiple myeloma in remission after induction?
## NCI PRO-CTCAE Study Group

Supported through NCI contracts HHSN261200800043C and HHSN261201000063C

<table>
<thead>
<tr>
<th>Ethan Basch</th>
<th>Catherine Coleman</th>
<th>Paul Kluetz</th>
<th>Katherine Ramsey</th>
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<tr>
<td>Sandra Mitchell</td>
<td>Stephanie Consoli</td>
<td>Reshma Koganti</td>
<td>Bryce Reeve</td>
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<td>Amy Abernethy</td>
<td>Cori Couture</td>
<td>Edward Korn</td>
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<td>Jeff Abrams</td>
<td>Andrea Denicoff</td>
<td>George Komatsoulis</td>
<td>Dave Rothfarb</td>
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<td>Suneel Allareddy</td>
<td>Amylou Dueck</td>
<td>Virginia Kwitkowski</td>
<td>Sean Ryan</td>
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<td>Benjamin Arnold</td>
<td>Jana Eisenstein</td>
<td>Suzanne Lechner</td>
<td>Daniel Satele</td>
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<td>Pamela Atherton</td>
<td>Maria Fawzy</td>
<td>Lauren Lent</td>
<td>Martin Schoen</td>
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<td>Thomas Atkinson</td>
<td>Shanda Finnigan</td>
<td>Yuelin Li</td>
<td>Deborah Schrag</td>
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<td>Natalie Barragan</td>
<td>Steve Friedman</td>
<td>Carol Lowenstein</td>
<td>Ann Setser</td>
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<td>Paul Baumgartner</td>
<td>Joshua Gagne</td>
<td>Donna Malveaux</td>
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<td>Lauren Becker</td>
<td>Vinay Gangoli</td>
<td>Michael Mejia</td>
<td>Mary Shaw</td>
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<td>Antonia Bennett</td>
<td>Marcha Gatewood</td>
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<td>Marwan Shouery</td>
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<td>Laurie Burke</td>
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<td>Diane St. Germain</td>
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<td>Mehul Gulati</td>
<td>Ann O'Mara</td>
<td>Ann Marie Trentascosti</td>
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<td>David Cella</td>
<td>Gaurav Gupta</td>
<td>Diane Paul</td>
<td>Ted Trimble</td>
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<td>Alice Chen</td>
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<td>Steven Clauser</td>
<td>Jessica Hess</td>
<td>Barbara Perez</td>
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<td>Charles Cleeland</td>
<td>Lori Hudson</td>
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<td>Gordon Willis</td>
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<td>Norval Johnson</td>
<td>Liora Pollick</td>
<td>Jennifer Wind</td>
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- **Organizational Affiliations:** NCI Community Cancer Centers Program (NCCCP), RTOG, Alliance, FDA
- We gratefully acknowledge our study participants and patient representatives!
Optimizing Dosing of Oncology Drugs

Oliver Rosen, M.D.
Millennium: The Takeda Oncology Company
A New Window of Opportunity

• Promising data from registration-directed studies trigger the desire for early drug access

• **Time from data presentation until the commercial launch represents a window of opportunity for additional data collection**
  – Expanded access programs usually the only way for early access
  – Dosing optimization study attractive due to lack of placebo arm

• Timing of dosing optimization studies is important

• Collaborative assessment of dosing optimization data will be based on surrogate endpoints e.g. response rate
What does it take for such an approach to succeed?

- Approach requires a close collaboration between FDA and a sponsor
- Review of supplemental dosing data should not lead to
  - A delay of the PDUFA date
  - Require a supplemental BLA
- Two approaches are conceivable regarding timing of dosing optimization studies
The Two Potential Approaches

• After (high-level) release of promising data e.g. press release of promising data a registration-directed study
  – Not realistic to provide exposure data in time without delaying the PDUFA date
  – Will most likely require a supplemental BLA

• Earlier activation e.g. following an milestone of a registration-directed study to ensure consideration of data during FDA review process
  – Will ensure a review of exposure data in time without delaying the PDUFA date
Second Window of Opportunity … Two Possibilities

<table>
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<tr>
<th>Phase I ± Phase II</th>
<th>R-studies</th>
<th>Filing &amp; Review</th>
<th>Commercial Access</th>
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<td>Identification of dosing regimen for R-studies</td>
<td>Dosing optimization</td>
<td>Dosing optimization*</td>
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*A would need to allow for consideration in initial product label*
Second Window of Opportunity … Two Possibilities

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Compared to the traditional approach

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<td>Dosing optimization as Post-Marketing commitments</td>
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Comparison of Study Timelines with Window of Opportunity

Phase I ± Phase II  | R-studies  | Filing & Review  | Commercial Access

Identification of dosing regimen for R-studies  |  | Dosing optimization  |  

⇒ Approach A would require delay of PDUFA date or a supplemental BLA

Press Release

Submission

Time (Months)

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<th>14</th>
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<tr>
<td>Filing</td>
<td>FDA Review Period (assuming priority review)</td>
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<tr>
<td>Enrollment period</td>
<td>Minimum Follow up (3 months)</td>
<td>Database lock</td>
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Conclusion

• As outlined by Dr Rahman, several recently approved oncology drugs are indicated for the use with suboptimal doses

• Both approaches for additional data collection during second window of opportunity have its pro’s & con’s

• Benefits of the option of delayed dosing optimization studies
  – Increased flexibility for sponsors due to a second, later window of opportunity for dose comparisons
  – Opportunity to further refine the dosing & administration section of a product label while pivotal studies are ongoing
  – Dose or scheduling comparisons could be based on surrogate endpoints and not the primary endpoint of ongoing pivotal studies
  – Reduction in post-marketing commitments
Optimizing Dosing of Oncology Drugs

Richard Pazdur, M.D.
Office of Hematology and Oncology Products, FDA