Oncology Drug Development: Phase I Case Studies in Healthy Volunteers

Mike Di Spirito, MSc
22-March-2018 ASCPT
Overview

- Tobacco – cancer - biomarkers of exposure
- Interesting science – using healthy normal volunteers to mimic the diseased state
- Celerion’s early phase oncology small molecule experience in healthy normal volunteers
  - Case studies
Smoke/Vape

The lesser of 2 evils?
Tobacco Use Is the Single Largest Preventable Cause of Death in the US

Cancer – bladder, cervix, esophagus, kidney, larynx, leukemia, lung, oral cavity, pancreas, stomach
Cardiovascular disease – atherosclerosis, stroke, coronary heart disease
Respiratory disease – COPD, pneumonia, impaired lung development and growth, impaired pulmonary function, poor asthma control
Reproductive effects – SIDS, infertility, low birth weight, pregnancy complications
Others – cataracts, diminished health status, low bone density, hip fractures, peptic ulcer disease
Cancer of the Voice Box - Larynx

- Traditional Therapy
  - Surgery
  - Laser Therapy
  - Radiation Therapy
  - Chemotherapy
    - Typically parenteral admin
    - Non-specific target
    - Serious dose- and duration-limited Aes
    - Can produce secondary malignancies
Cigarette Smoke Components

Harmful and Potentially Harmful Constituents
Cigarette Smoke Components

Nicotine → Cotinine → 3-HC

NNN → NNAL

PAH (Polycyclic Aromatic Hydrocarbons)

VOC’s (Volatile Organic Compounds)

1, 3-Butadiene → Acrolein → Benzene → Ethylene oxide

© 2014 American Association for Cancer Research

Cancer Research Surgeon General’s Report
<table>
<thead>
<tr>
<th>Exposure Component</th>
<th>Measured Analyte</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOOD</strong></td>
<td></td>
</tr>
<tr>
<td>Nicotine</td>
<td>Nicotine, cotinine, trans-3'-Hydroxycotinine</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>Carboxyhemoglobin</td>
</tr>
<tr>
<td><strong>URINE</strong></td>
<td></td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>Dihydroxybutylmercapturic acid, monohydroxybutenylmercapturic acid</td>
</tr>
<tr>
<td>Acrolein</td>
<td>3-Hydroxypropylmercapturic acid</td>
</tr>
<tr>
<td>Aldehydes</td>
<td>Acetaldehyde, formaldehyde</td>
</tr>
<tr>
<td>Benzene</td>
<td>S-phenyl mercapturic acid</td>
</tr>
<tr>
<td>Benzo[a]pyrene</td>
<td>3-hydroxybenzo[a]pyrene</td>
</tr>
<tr>
<td>Crotonaldehyde</td>
<td>3-Hydroxy-1-methylpropylmercapturic acid</td>
</tr>
<tr>
<td>Nicotine Equivalence</td>
<td>Nicotine, cotinine, trans-3'-hydroxycotinine, nicotine-N-glucuronide, cotinine-N-glucuronide, trans-3'-hydroxycotinine-O-glucuronide</td>
</tr>
<tr>
<td>Pyrene</td>
<td>1-Hydroxypyrene</td>
</tr>
<tr>
<td>Tobacco-Specific Nitrosamines</td>
<td>NNAL, NNN, NAB, NAT</td>
</tr>
<tr>
<td>Polyaromatic Hydrocarbons</td>
<td>1- and 2-hydroxynaphthalene; 2-hydroxyfluorene; 1-, 2-, 3-, 4-, and 9-hydroxyphenanthrene</td>
</tr>
<tr>
<td>Aromatic Amines</td>
<td>3- and 4-aminobiphenyl, o-toludine, 2-aminonaphthalene</td>
</tr>
<tr>
<td>Urine Mutagenicity</td>
<td>Ames Test</td>
</tr>
</tbody>
</table>
Forced Switch Study in Smokers

- Forced-switch parallel proof-of-concept study
- Assessed exposure to biomarkers of tobacco exposure following short-term ad libitum use of 3 electronic products vs dual (regular + electronic) vs cessation.
- Baseline measurements - regular cigarettes on Day -1
- Switch - Post-product use measurements Days 1-6
- Change from baseline in biomarkers of exposure presented after 5 days
Change in Urine Biomarkers of Exposure After 5 Days


N = 103
Tobacco Product Risk Continuum

HIGH

Conventional Cigarettes

Tobacco Heating Products (THPs)

Low-toxicant Smokeless Tobacco

VAPOUR PRODUCTS (E-CIGARETTES)

LICENSED MEDICINAL PRODUCTS

LOW

Tobacco products that involve no combustion

Nicotine products that contain no tobacco and involve no combustion
Impact of Tobacco Use

- Tobacco induces CYP1A
- Constitutive activity of CYP1A low in normal individuals, however substantially upregulated
- If preclinical testing suggests CYP1A catalyzed metabolism: Consider testing in vivo, impact of smoking status on PK in early clinical pharmacology study before Phase II/III
- Mitigates risk of treatment failure in cancer patients who continue to smoke during treatment
The Giant
Acromegaly & Gigantism

- Usually caused by a noncancerous (benign) pituitary tumor – adenoma
- Overproduction of growth hormone
  - Tall stature, obesity
  - Macrocephaly
  - exaggerated growth of hands and feet, with thick fingers and toes
  - Coarse facial features
  - Wide spacing of the teeth
- Morbidity and mortality rates are high
  - Cardiovascular disorders
  - Cerebrovascular disorders
  - Respiratory disorders
  - Malignancies
Stimulation/Inhibition of GH

- Growth hormone-releasing hormone (GHRH)/arginine challenge (w/treatment/alone)
  - GHRH – IV bolus injection
  - Arginine Hydrochloride Injection – IV infusion over 30 minutes

- Somatostatin analogs used for therapy
  - Octreotide, Sandostatin, Somatuline

- Usual drug PK profiles (AUC, Cmax, Tmax, T1/2)
- PD – after challenge (AUEC, Emax, Tmax)
Typical GH Profile Post-Challenge (Induced) & Treatment (Suppression)
Early Phase Oncology Drug Development – Focus Change

Yesterday

![Cytotoxicity Sign]

Today

- Noncytotoxic oncology therapeutics
- Opportunity for HNS
- >60 studies (Celerion - since 2011) across variety of targets - VEGFR, EGFR, FGFR, MET, RET, BTK...
- FIH – SAD/MAD, DDI, NDA-enabling, BA, FE, Timing of meal, ADME, pH, TQT, cQT, RI, HI, Smoking effect, Palatability
Some kinase inhibitors are used to treat cancer.

Kinase inhibitors is a substance that blocks a type of enzyme called a kinase.

Human cells have many different kinases, and they help control important functions:
- cell signaling, metabolism, division, and survival

Certain kinases are more active in some types of cancer cells and blocking them may help keep the cancer cells from growing.

Kinase inhibitors may also block the growth of new blood vessels that tumors need to grow.
Kinase Inhibitors

- Inhibit Tyrosine/ Serine/ Threonine Kinases
- Most are orally bioavailable
- More specifically targeting overexpressed receptors and/or enzymes
- More selective for cancer cells vs. healthy cells
- Not without Adverse Event concerns
  - FIH starting dose
Considerations Before Testing Oncology Drugs in Healthy Subjects

General
- Mutagenicity/carcinogenicity
- Reproductive toxicity

Class Specific Concerns
- Skin rashes and other cutaneous reactions
- Hepatotoxicity
- Cardiovascular safety
- Gastrointestinal irritation (nausea/vomiting)
Developing Oncology Products: Phase I Timeline/Cost

- Estimates range from at least 12-18 months for n=25 oncology patients
- Compared to 4-6 months for healthy normal subjects (HNS)
- Patients studies can cost into the millions
- Targeted therapies alter the risk vs. benefit ratio relative to cytotoxic agents
- Unless compound causes direct DNA damage, FDA typically allows dosing in HNS
To Consider - Acid-Reducing Agents on PK of TKI Class Compound

- Use of Acid-Reducing Agents in Cancer Patients ranges from 20-70% across cancer types
- Not a class effect
- Similar to food-effect
  - Test early before patient studies
DDI - CYP3A4/P-gp Inhibition/Induction – Single Study

- Part A – Fixed Sequence
  - Drug SD – Itraconazole MD - Coadmin
  - Dose Drug Day 1
    - Drug PK, washout
  - Itraconazole MD, minimum 5 days and throughout sampling
  - Co-admin Drug+Itraconazole on Day 5 or later
    - Drug PK

- Part B – Fixed Sequence
  - Drug SD – Rifampin MD Coadmin with Drug SD on Days 1 and 10
  - Dose Drug Day 1
    - Drug PK, washout
  - Coadmin Rifampin SD with Drug SD
    - Drug PK, washout if necessary
  - Rifampin dosing for at least 10 days
  - Co-admin Drug+Rifampin on Day 10 or later
    - Drug PK
DDI - CYP3A4/P-gp Inhibition/Induction

MD Itraconazole

SD & MD Rifampin
Consider cQT Early in Development

- Exposure-Response Analysis will assess cardiac liability
- Data available across a series of doses
- Could come from SAD/MAD/DDI/High Exposure studies
- Data could be collected, stored, analyzed at a later date
Data Allows for Evaluation of cQT - Change From Baseline in QTcF vs Time-Matched Concentrations
The Total Radioactivity concentration-equivalent vs time plot is a sum plot of drug + all of its RA metabolites.

- Observed total RA Cmax ≥ Drug Cmax
- Estimated total RA AUC0-inf ≥ Drug AUC0-inf
- Estimated total RA terminal t1/2 ≥ Drug terminal t1/2
Plasma Profile

Dose Recovered

ADME/Mass Balance

Time

(ng eq/mL)

TRA
Parent Drug

%DoseU
%DoseF
Total

Time

%DoseU
%DoseF
Total
Oncology Drug Development – HI/RI

\[
\text{[Drug]} \text{ (ng/mL)}
\]

\[
\text{Time}
\]

- Severe HI/RI
- Moderate HI/RI
- Mild HI/RI
- HNS
In Summary

- Development of noncytotoxic oncology therapeutics in the last decade has increased and is now the norm
  - Opportunity to test on HNS rather than patients
  - Opportunity to use classic Phase I designs
  - Shorter study timelines from start to finish
  - Robust characterization of PK
  - Lower costs per study

- Celerion has experience in all aspects of early phase development for your new oncology drug

- Together, we can beat it!
Thank you!

Questions?