Drug-Drug Interaction (DDI) Screening for Oncology Clinical Trial Enrollment

Dan Hertz, PharmD, PhD
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Oishi Symposium
SWOG Spring 2019
Outline

• PK and PD Drug-drug Interactions

• DDI Screening

• SWOG DDI Screening Initiative
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Pharmacokinetics (PK) and Pharmacodynamics (PD)

**Pharmacokinetics (PK)**
- PK: amount of drug in the body
  - “what the body does to the drug”
- PK determined by ADME processes
  - Absorption
  - Distribution
  - Metabolism
  - Excretion

**Pharmacodynamics (PD)**
- PD: bodies response to drug
  - “what the drug does to the body”
- PD determined by interaction of drug with targets (receptors)
  - On-target effects: efficacy
  - Off-target effects: toxicity
Blood (Circulation)

Intestine

ADMINISTRATION
Absorption
Distribution
Metabolism
Excretion

Blood (Circulation)

Tumor
Heart
Lung
Brain

Liver
Kidney
Intestine

ELIMINATION
ADMINISTRATION

PK
Drug Interactions

• Drug interactions:
  • “A situation in which a substance affects the activity of a drug when both are administered together”
  • Focus on drug-drug interactions (DDI) but others exist:
    • Drug-food interactions
    • Drug-gene interactions (pharmacogenetics)

• DDI influence the relationship between dose and response
  • Pharmacokinetic (PK) relationship: amount of drug in body
  • Pharmacodynamic (PD) relationship: body response to drug
Passive Absorption DDI

- Some drugs require acidic environment in stomach/intestine for absorption
  - Oral tyrosine kinase inhibitors such as dasatinib

- Antacids make stomach/intestine less acidic and can inhibit drug absorption
  - Maalox, Pepcid/famotidine, Prilosec/Omeprazole
  - Note most of these are over the counter meds

- Protocols can warn to avoid:
  - “Acid suppression”
  - “Drugs that increase gastric pH”

Eley T et al., J Clin Pharmacol. 2009 PMID: 19395585
Active Absorption/Distribution DDI

- Most drugs are actively absorbed and distributed around the body via drug transporters
  - P-gp, ABCB/ABCC, MDR, OAT/OCT, SLCO

- Some drugs inhibit or induce transporters
  - Inhibitors DECREASE transport
  - Inducers INCREASE transport

- Protocols may recommend avoiding:
  - “Inhibitors of p-glycoprotein (P-gp)”
  - “Inducers of OATP1B3”

- We have limited knowledge of transporters and their DDI, relative to enzymes

McLeod HL. Br J Clin Pharmacol. 1998 PMID: 9663808

MTX alone (●)
MTX w/probenecid (○)
Metabolism DDI

• Most drugs are metabolized by enzymes
  • Drug referred to as a “substrate” of that enzyme
    • i.e., CYP3A4, CYP2D6, UGT1A1, SULT1A1

• Many drugs inhibit or induce enzymes
  • Inhibitors DECREASE metabolism
  • Inducers INCREASE metabolism

• Protocols may recommend avoiding:
  • “CYP3A4 substrates”
  • “CYP2D6 inducers”
  • “UGT1A1 inhibitors”

• We have extensive knowledge of enzymes and their DDI

Tumor Heart Lung Brain

PD EFFICACY TOXICITY

Blood (Circulation)

Liver Kidney Intestine

Receptor

ELIMINATION
PD DDI

• PD: The body response to the drug

• PD DDI occur when drugs taken together have effects that are similar (additive) or opposing (antagonistic)
  • Similar effects enhance efficacy or toxicity
  • Opposing effects offset efficacy or toxicity

• Most often concerned about additive toxicity
  • i.e., additive sedation (sleepiness) or QT prolongation (heart arrhythmia)
  • “Avoid drugs that cause QT prolongation”

• We could also be concerned about opposing efficacy
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DDI Severity and Relevance to SWOG ORP

Severity (in general, no single scale)

- Contraindicated
  - Drugs should never be co-administered
  - Confirmation of likely severe harm

- Major
  - Drugs should not be co-administered
  - Strong likelihood of severe harm

- Moderate
  - Co-administration should be avoided if possible
  - Possibility of harm

- Minor
  - Co-administration likely ok
  - Theoretical risk considered not to be clinically relevant

Relevance to SWOG

- SWOG Study Subjects
  - Increased toxicity
  - Decreased efficacy

- SWOG Trial Data
  - Inaccurate estimates of efficacy and/or toxicity from trials
DDI Screening

• Standard practice in medical care
  • Often pharmacists’ responsibility
  • Built into electronic medical systems
    • Prescription systems at pharmacy
    • Electronic medical records at hospital

• DDI in Oncology Patients
  • Study of Dutch oncology patients (n=278)
    • 161 patients (58%) had at least one DDI
    • 348 total DDI detected
      • 34% major, 60% moderate
      • 40% involved anticancer drug

van Leeuwen RW, Ann Oncol. 2011 PMID: 21343376
Nurse’s Role and Confidence in DDI Screening

- Surveys of nurses suggest:
  - Nurses often encounter DDI
    - 23% in last year
  - Nurses often responsible for teaching patients about DDI
    - 45%-50%
  - Nurses lack confidence in their DDI knowledge
    - 23%

Table 2 Mean performance

<table>
<thead>
<tr>
<th>Area tested</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>28.6</td>
</tr>
<tr>
<td>Indications</td>
<td>72.6</td>
</tr>
<tr>
<td>Contraindications</td>
<td>57.1</td>
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<tr>
<td>Normal adult dose</td>
<td>78.6</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>22.6</td>
</tr>
<tr>
<td>Side effects</td>
<td>79.8</td>
</tr>
<tr>
<td>Nursing assessment</td>
<td>51.2</td>
</tr>
</tbody>
</table>

Ndosi ME. J Clin Nurs. 2009

Karahan A, Asia Pac J Oncol Nurs. 2015
DDI Screening Tools

• Flockhart Table of CYP enzyme substrates/inhibitors/inducers
  • https://drug-interactions.medicine.iu.edu/main-table.aspx

• Subscription Tools
  • Lexicomp
  • Micromedex

• Free Tools
  • Drugs.com
  • WebMD

• Our study of screening 145 Oncology DDIs with 9 tools
  • Lexicomp had best information
  • Drugs.com is free and performed similar to Lexicomp
DDI Screening for Oncology Trials

• Recent editorial: all oncology clinical trial subjects need to be screened for DDI by a pharmacist during enrollment
  • McGahey KE et al. Am J Health-Syst Pharm 2017 PMID: 28389457

• Screening should be conducted:
  • At enrollment to screen current medications
  • At each evaluation or at the time of any medication changes

• Screening should be based off information in protocol
  • Responsibility of PI (and SWOG Pharmaceutical Sciences Committee) to ensure that DDI information in protocol is accurate and complete
DDI Information in Clinical Trial Protocols

- Lack of uniformity in location of information, terms used etc.
  - Information can conflict within sections of a single protocol
- Protocol sections that include DDI Information
  - Drug Information (Sec 3): Potential Drug Interactions
    - Discusses mechanism and data
  - Exclusion criteria (Sec 5)
    - Drugs, classes, or PK/PD mechanisms (i.e. 3A4 inducers, QT prolongation)
  - Treatment Plan (Sec 7): Concomitant Medications
    - Recommendations for exclude, avoid, use with caution
- Prohibited Medications List
  - Usually table of substrates, inhibitors and/or inducers, like Flockhart Table
DDI Survey of SWOG Head CRAs

- 78 Responses (~160 Invited)
  - 55% Community hospital/outpatient
  - 29% Academic teaching hospital
  - 4% Non-academic hospital
  - 4% VA hospital
  - 1% Private practice infusion center
  - 8% Other (Military, HMO, NCORP office)
How often are DDI screened for potential subjects to assess their eligibility to enroll on a SWOG trial?

- **Always**: 39%
- **Sometimes**: 8%
- **Only when an exclusion criteria**: 53%
- **Never**: 0%

≈50% of sites screen DDI ONLY when required by exclusion criteria

Hertz DL. Am J Health-Syst Pharm. 2018 PMID: 29748299
Who Screens DDI during SWOG Eligibility Assessment?

- PI/MD
- CRA
- Res. Nurse
- Staff Nurse
- PharmD
- Other

DDI screened by ORP staff with diverse medical training

Hertz DL. AJHP 2018
How often are the following resources used for DDI screening?

Some sites have advanced DDI resources (i.e. electronic CDS)

Others lack basic drug information resources (Pharmacist, Lexicomp)

Hertz DL. AJHP 2018
DDI In Oncology Clinical Trial Subjects

- 291 patients prospectively screened for 4 NCI phase I trials
  - 3.2% (n=7) excluded due to DDI
  - 74 subjects enrolled
    - 69% (n=51) had ≥1 DDI identified and managed
    - 93 total DDI managed:
      - Medication stopped (41%) or changed (44%)

- 128 Patients enrolled on NCTN studies at UM
  - 24% had major DDI w/study drug
  - 9% had clinically relevant DDI w/study drug

Wisinski KB, Am J Health Syst Pharm, 2015, PMID: 25987691
Marcath LA, BMC Cancer 2018, PMID: 30466416
DDI in SWOG Subjects

• SWOG trials of agents w/DDI and concomitant med info
  • S0711 (dasatinib)
  • S0528 (lapatinib)

• N=163 patients enrolled
  • 31% had ≥1 major DDI
  • 16% had ≥1 clinically relevant DDI
    • All affected study agent

• DDI rates similar to UM pilot
Summary of DDI Background

• High prevalence of DDI in oncology patients and clinical trial subjects
  • Concerning for patient safety and SWOG clinical trial data accuracy

• Processes for DDI screening are inconsistent and ineffective
  • DDI screening conducted by various staff, when conducted at all
  • Pharmacist-led screening may be ideal, but is impractical

• Critical need to equip all SWOG sites with user-friendly tool for efficient, appropriate, and uniform DDI screening
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SWOG DDI Screening Initiative

Overall goal

• Reduce DDI in patients enrolling on oncology clinical trials to enhance efficacy, prevent toxicity, and ensure accuracy of clinical trial data

Project Objectives

1. Develop clinical trial DDI screening tool
2. Assess user satisfaction during implementation pilot
3. Demonstrate benefit in implementation study
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SWOG-PEPID DDI Screening Tool

- Web-based tool for DDI screening
  - [PEPID.com/SWOG](PEPID.com/SWOG)

- Can be made accessible to all SWOG ORP

- Specific functionalities for oncology trial DDI screening
Filter results to show interactions impacting only the study agent, all involving the study agents, or all combinations of interactions.

Filter by severity and display all details of the interaction.

Export pdf that includes all entered information and displays results based on filter selections.

Future iterations to incorporate investigational agents, additional medication characteristics, and automatic import of concomitant medications from EMR.

Displays characteristics of the “Current Med List” medications.

Select medication characteristics to display for comparison with protocol guidance.

Concurrent entry of all concomitant meds.

Separates trial and concomitant medications.
Displays trial drugs and medication list that was input

Shows only interactions that were displayed based on selected filter settings

Shows medication characteristics that were selected
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PEPID Implementation Pilot at UMCCC

Methods:

• Provide PEPID tool to 2 NCTN data managers
  • Including training video and instructions document
• Use during enrollment screening for 3 months
• Feedback collected from data managers via phone call
  • Determine usability and perceived usefulness
## Pilot Implementation Data Manager Feedback

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<tr>
<th>Strengths</th>
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<td>Easy to use</td>
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<td>Increased screening efficiency (1hr -&gt; 10 min)</td>
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<td>Great for screening CYP450 interactions</td>
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<td>PDF export useful to convey information</td>
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- **Strengths**
  - Easy to use
  - Increased screening efficiency (1hr -> 10 min)
  - Great for screening CYP450 interactions
  - PDF export useful to convey information

- **Weaknesses**
  - Missing some pharmacodynamic interactions (i.e. antiarrhythmic agents)

- **Approach to Resolve Weakness**
  - Add additional pharmacodynamic interactions to the Medication Characteristics panel

- **Strengths**
  - Increased screening efficiency (1hr -> 10 min)

- **Weaknesses**
  - Provider confusion about interpreting PDF report

- **Approach to Resolve Weakness**
  - Filter PDF report and tool for level 3+ interactions
  - Move Medication Characteristics summary to top of report
PEPID Implementation Expansion Study

• Objective
  • Test PEPID implementation at ~10 diverse SWOG sites
    • Different institutional settings, workflows, staff roles

• Methods
  • Identify sites that are interested in using tool (TODAY!)
  • Provide training video, instructions, and PEPID login information
  • ORP staff use tool for ~ 3 months
  • Collect feedback from ORP staff via survey and brief telephone interview
Sites Interested in Participating in Pilot

• Looking for 10 diverse sites
  • Community cancer centers
  • Academic teaching hospitals
  • Non-academic hospitals
  • VA hospitals
  • Private practice offices
  • NCORP Sites

• If you are interested in participating contact me!!!!
  • Come talk to me at ORP Open Forum (today 12-2:30, PMB table)
    • Can watch instructional video and test tool
  • E-mail me: Daniel L Hertz, University of Michigan, DLHertz@umich.edu
    • Include type of SWOG site you represent
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PEPID Implementation Trial within SWOG

- Multi-site implementation trial of PEPID within SWOG
  - To be developed within Cancer Care Delivery Committee

- Select (n=50?) SWOG sites across diverse practice settings
  - Use tool within SWOG trials
  - Compare DDI screening pre-/post- implementation

- Study objective: to demonstrate improvement in DDI screening
  - Less time spent screening DDI during enrollment
  - Fewer DDI in patients enrolled on trials
  - Reduced DDI-related adverse events (?)
Test Case for PEPID-SWOG Tool: S1913

• S1913: A Randomized Double-Blind Phase II trial to improve sexual desire in women with cancer
  • Study agent is flibanserin

• Flibanserin has multiple contraindications:
  • Moderate/strong CYP3A4 inhibitors (PK DDI)
    • Increased hypotension and fainting risk
  • Alcohol (PD DDI)
    • Additive hypotension and fainting risk

• Protocol in development includes PEPID Tool for enrollment DDI screening
SWOG DDI Screening Initiative Summary

• 1st Generation PEPID-SWOG DDI Screening Tool Created

• Single-center implementation pilot completed
  • High user satisfaction

• Looking for sites for multi-center expansion pilot (DLHertz@umich.edu)
  • Feedback critical for improvements and to determine next steps

• Prospective implementation studies anticipated to confirm usefulness

• We would greatly appreciate ORP feedback regarding the project, PEPID tool, how the tool fits into your workflow, and anything else!
Questions?
Dan Hertz, PharmD, PhD
DLHertz@med.umich.edu