Research in Older Patients: Drug Interactions and Pharmacology Monitoring

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Faculty Disclosures

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Objectives

1. Evaluate recent literature on the prevalence and consequences of drug interactions in older adults with cancer

2. Discuss potential research opportunities that can advance the literature on drug interactions
A drug-drug interaction  -  A pharmacologic/clinical response that occurs when the administration of one drug alters the effects of another.

Are all drug interactions harmful?
• Some drug interactions are beneficial – e.g., interaction between fluorouracil and folinic acid (leucovorin) enhances the anti-tumor activity of fluorouracil [Category C]

## Drug Interaction Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Mechanism</th>
<th>Example</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-drug (Pharmacokinetic)</td>
<td>The concentration of a drug is influenced by another drug due to absorption-distribution-metabolism-elimination. ↓ absorption of erlotinib due to ↑ stomach pH from omeprazole</td>
<td>Erlotinib + Omeprazole [Category X]</td>
<td>Treatment failure (e.g., cancer progression, mortality)</td>
</tr>
<tr>
<td>Drug-drug (Pharmacodynamic)</td>
<td>Related to the drugs effect on the body – may be additive, synergistic or antagonistic. Co-administration of trastuzumab may enhance the cardiotoxic effects of anthracyclines</td>
<td>Doxorubicin + Trastuzumab [Category D]</td>
<td>Treatment toxicity (e.g., increased risk of cardiac dysfunction and heart failure)</td>
</tr>
</tbody>
</table>

Drug Interactions: Pharmacokinetics

Liver
Metabolism in the liver by CYPs (potential site for drug interactions)

Stomach
Absorption in the gut depends on the presence or absence of food on pH

Circulation
Transportation in the blood

Kidney
Excretion in the kidney (potential site for interactions with transporters and proteins)

Intestine

CYPs, cytochrome P450 enzymes; CYP3A4, cytochrome P450 3A4.
## Additional Drug Interaction Categories

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<th>Category</th>
<th>Example</th>
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<tr>
<td>Drug-food</td>
<td>Palbociclib + Grapefruit</td>
<td>Eating grapefruit and/or grapefruit juice with palbociclib can increase the blood levels of palbociclib through CYP450 enzyme inhibition in the gut [Category X]</td>
<td>Increased toxicity (e.g., nausea/vomiting, diarrhea, myelosuppression)</td>
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<tr>
<td>Drug-herbal</td>
<td>Irinotecan + St. John’s Wort</td>
<td>Using irinotecan with St. John’s Wort leads to lowered levels of the irinotecan metabolite (SN-38) by as much as 40% [Category X]</td>
<td>Reduced efficacy (e.g., decreased levels of irinotecan, reduced effectiveness)</td>
</tr>
<tr>
<td>Drug-disease</td>
<td>Cisplatin + chronic kidney disease</td>
<td>Cisplatin can cause pre-renal perfusion deficits and/or direct tubular damage to kidney vasculature</td>
<td>Treatment toxicity (e.g., acute kidney injury, worsening chronic kidney disease)</td>
</tr>
</tbody>
</table>

Drug Interactions in Patients Enrolled on National Clinical Trials Network Oncology Clinical Trials
# Drug-drug Interaction (DDI) Trials: Geriatric Oncology

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>Median Age (yrs.)</th>
<th>Screening Method</th>
<th>Sample size, Prevalence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019; Beinse</td>
<td>Retrospective secondary analysis; DDI in older adults</td>
<td>77 (r: 74-80)</td>
<td>Lexicomp™, Theriaque™ (French medications)</td>
<td>N = 442 338 (76.5%)</td>
<td>High prevalence of DDI; cardiovascular comorbidities were more likely to have a PDI*; high number of PDIs was associated with risk of unplanned hospitalization</td>
</tr>
<tr>
<td>2018; Nightingale</td>
<td>Retrospective secondary analysis; DDI in older adults</td>
<td>78 (r: 65-101)</td>
<td>Lexicomp™, Micromedex™</td>
<td>N = 142 98 (69%) 87 (61%)</td>
<td>High prevalence of DDI; variability exists between detection software; need to better determine the relevance and clinical implications of DDI</td>
</tr>
</tbody>
</table>
Have Drug Interactions Impacted Survival in Older Adults with Cancer?

- Retrospective study (Medicare data, 2007 through 2012)
- N=12,538 (median age 76) [lung, liver, renal, pancreas, CML]
- Prevalence of TKI-PPI interactions were 22.7%
- TKI-PPI DDI is associated with ↑ risk of death at 90 days and 1 year
- Polypharmacy was a predictor of concomitant TKI-PPI use
Drug Interactions: Pharmacokinetic effects of acid suppressive agents on TKI absorption

No DDI
- Cobimetinib
- Crizotinib
- Cabozantinib
- Imatinib
- Osimertinib
- Vandetanib
- Axitinib
- Dabrafenib
- Ponatinib
- Regorafenib
- Ibrutinib
- Lenvatinib
- Sorafenib
- Vemurafenib
- Trametinib
- Afatinib
- Ruxolitinib

DDI:
- Ceritinib
- Gefitinib
- Erlotinib
- Dasatinib
- Pazopanib
- Nilotinib
- Lapatinib
- Bosutinib
- Alectinib
- Sunitinib
- Nintedanib
- Tivozanib
What Potential Drug Interactions Exist with Newer Agents like CDK 4/6 Inhibitors?

CYP3A4 inducers +Anticonvulsants (e.g., carbamazepine) +Antibiotics (e.g., rifampin) +Herbal medicines (e.g., Hypericum p.)

CYP3A4 inhibitors -Antibiotics (e.g., clarithromycin) -Antifungals (e.g., ketoconazole) -Diet (e.g., grapefruit juice)

CDK 4/6 inhibitors Oral administration

PK profiles and outcomes

Inhibition of drug metabolism

No DDI Therapeutic window Clinical benefit

Increased risk of toxicity

Induction of drug metabolism

Increased risk of drug failure

Time (hours)
What’s lacking? Potential research opportunities

• Standards and guidance recommendations for screening, characterizing and managing drug interactions are lacking
  • Conflicts and discrepancies exist among drug compendia with regard to severity and scientific evidence ratings

• There is not a high priority list of drug interactions that are evidence-based, clinically significant and agreed upon by oncology experts

• Robust research is still needed with a focus on the clinical significance and consequences of DDI (e.g., clinical outcomes)
  • Are the interactions associated with a drug-class effect?
  • There are no best practices for managing DDI utilizing de-prescribing
The Role for Therapeutic Drug Monitoring with Oral Oncolytics: Example of Pazopanib

- **Start treatment at standard fixed dose** (e.g., 800 mg QD for pazopanib)
- **PK sampling after 4, 8 and 12 weeks; and every 12 weeks thereafter**
- **Adequate PK** (e.g., C_{min} ≥ 20.5 mg/L for pazopanib)
- **Low PK** (e.g., C_{min} < 20.5 mg/L for pazopanib)

**Dose level** | **Pazopanib dose**
--- | ---
-3 | 200 mg QD
-2 | 400 mg QD
-1 | 600 mg QD
0 | 800 mg QD
+1 | 400 mg BID
+2 | 400 mg BID + food
+3 | 400 mg / 600 mg + food
+4 | 600 mg BID + food
+5 | 600 mg / 800 mg + food
+6 | 800 mg BID + food
+7 | 800 mg / 1000 mg + food
+8 | 1000 mg BID + food

**Toxicity**
- Continue at same dose level
- Reduce one dose level
- Increase one dose level
- Continue at same dose level or reduce one dose level