If I'm So Smart, Why Can't I Manage Drug Interactions?

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Mitigating Potential Bias

- Not Applicable

Objectives

- Identify common drug interactions in oncology
- Become more confident managing drug interactions in oncology patients
- Make meaningful recommendations regarding drug interactions

Setting the Stage

- A drug-drug interaction is a pharmacokinetic or pharmacodynamic influence of one drug on another, which can reduce the effectiveness of one or both of the interacting drugs or can lead to toxic effects.[1]
- It is estimated that drug interactions cause up to 2.8% of hospital admissions, and they can lead to serious adverse outcomes for patients. [1]
- 20-30% of all adverse effects are attributed to drug-drug interactions in the general population.[2]
- Drug interactions are estimated to be the cause of death in 4% of cancer patients. [2]

Setting the Stage

- A retrospective review of potential drug interactions and toxicity in older patients receiving chemotherapy found[3]:
  - Potential drug interactions in 75% of patients
  - Risk of non-hematological toxicity increased by 17% for each additional potential major/moderate interaction
  - Risk of non-hematological toxicity increased by 29% for each additional potential drug interaction involving chemo
- Authors recommend that oncologists carefully review and trim down the list of medications that older patients are on, before initiating chemotherapy[3].

Can you spot the interaction?

- About half of drug interactions were correctly identified by physicians in one study.
- New drugs being added so quickly it's difficult to remember important interactions.
- We rely on automated databases to identify drug interactions.
- These systems may fail to identify up to one third of interactions, while alerting pharmacists to trivial interactions, leading to alert fatigue. [4]

More Challenges

- Many drug interactions are identified in oncology patients; determining management strategy is difficult since treatments often can not be modified.
- Cancer drugs are known to have narrow therapeutic indexes
  - increased levels may cause significant toxicity and patient harm
  - decreased levels may lead to under treatment which is impossible to detect

Common Drug Interactions in Oncology

- Tamoxifen and antidepressants
- Bortezomib and green tea
- Hydrochlorothiazide and fluorouracil or cyclophosphamide
- Warfarin and fluorouracil/capecitabine
- Pemetrexed and NSAIDs
- Phenytoin and cyclophosphamide
- Ibrutinib (CYP3A4 substrate)
- Idelalasib (CYP3A4 substrate)
- Cobimetanib (CYP3A4 substrate)
- Dabrafenib (CYP3A4 and 2D6 substrate)
- Vemurafenib (substrate and inhibitor of p-glycoprotein, substrate and inducer of 2D6 and 2C9)
- …

What's a Pharmacist to do?

- Drug interaction screening in ARIA
  - Med History must be updated regularly
  - Natural products may not be documented
  - Natural products may not be screened by automated tools
- Search DPIN to look for other meds not documented
- Use additional drug interaction screening tools (Micromedex, Lexi-Comp)
- If using multiple tools, variable results occur.

Develop a Strategy[5]

1. Identify the interaction:
   - Consider drug specific factors
   - Consult more than one interaction checker
2. Interpret the information:
   - Evidence (specificity, how robust, one case or multiple)
   - Nature of interaction (dose related, timing related, expected)
   - Magnitude of effect (time of onset, narrow TI, treatment outcome, ability to monitor)

Strategy Continued

3. Predict likelihood of interaction and Determine Clinical Significance:
   - Consider patient factors such as age, underlying disease states, efficacy of current regimen, adverse effects
   - Does this affect all patients on this drug, or just this one?
4. Action:
   - Make a patient specific recommendation
5. Report to physician:
   - Organized manner
   - Brief summary of important observations
   - Clear recommendation with rationale to support the recommendation
6. Document in the patient record

Case 1

TD is a 55 year old woman with hormone sensitive breast cancer. She is starting on tamoxifen for five years. Upon review of her medication, you see that she is also on paroxetine 40 mg daily, which is flagged as a major interaction in Micromedex.

What do you do?

1. Recommend that she discontinue her paroxetine.
2. Recommend that she monitor for toxicity.
3. Recommend a switch in antidepressant.
4. Do nothing. Assume the oncologist is aware.

Tamoxifen Activity[6]

- Tamoxifen is metabolized to its active metabolite (endoxifen) by CYP2D6.
- Moderate to strong CYP2D6 inhibitors given with tamoxifen would reduce it's effectiveness in preventing cancer recurrence.
- Some studies have shown earlier relapse and reduced overall survival in women who took CYP2D6 inhibitors; other studies have failed to find any effect.
  - Evidence is conflicting; challenges with duration of follow up, difficulty in assessing adherence etc.

Tamoxifen Activity[6]

- Growing evidence that tamoxifen and endoxifen are substrates of p-glycoprotein, which might reduce tamoxifen bioavailability and efflux from cancer cells.
- Patients with more p-glycoprotein activity due to genetics or drug therapy would have reduced tamoxifen efficacy.
- Decreased CYP2D6 activity and increased p-glycoprotein activity may have additive effect in reducing tamoxifen activity.

Case 1 Recommendation

Summary:

- Robust evidence (clinical trials) on both sides
- Inability to monitor lack of effect
- Clinically significant outcome if drug interaction real
- There are other options (other SSRIs) without 2D6 activity.

✓ Recommend a change in therapy to another antidepressant such as citalopram, sertraline or venlafaxine

Tamoxifen and Antidepressants

https://www.crediblemeds.org/healthcare-providers/drug-drug-interaction/

a helpful list of preferred antidepressants for patients on tamoxifen

- bupropion, duloxetine, fluoxetine, paroxetine should not be taken concurrently with tamoxifen

Oral Anticancer Drugs

- Study of the prevalence of potential drug-drug interactions in patients on oral anticancer drugs[7].
  - Found 46% of patients were exposed to at least one potential drug interaction; 16% of these had at least one major interaction that may have had harmful side effects needing intervention or intensive monitoring.
  - 86% of interactions involved supportive care drugs (most frequent involved coumarins and fentanyl).
  - Majority of interactions included GI toxicity (risk of GI bleed), QT prolongation and CNS depression (risk of falls).

Case 2

LH is a 57 year old woman with recurrent ovarian cancer. She has ascites and is experiencing ongoing nausea. She has a history of high blood pressure and 'borderline' high blood glucose currently being managed with lifestyle changes.

Her home meds include:

venlafaxine XR 150 mg po bid

zopiclone 7.5 mg po hs

ranitidine 150 mg po bid

Bloodwork shows normal electrolytes.

Case 2

Oncologist orders ondansetron 8 mg po tid, olanzapine 2.5 mg daily and metoclopramide prn to help manage her nausea.

She is will be starting carboplatin and paclitaxel, which includes pre-meds of aprepitant, dexamethasone, diphenhydramine, ondansetron and ranitidine.

Case 2

Review of cycle 1 orders reveals the following interactions:

1. Additive QT prolonging drugs: olanzapine, venlafaxine and ondansetron are all drugs that can cause QT prolongation *major
2. Olanzapine and metoclopramide used together can increase the risk of extrapyramidal symptoms (EPS) and neuroleptic malignant syndrome (NMS). *contraindicated
3. Olanzapine and venlafaxine used together can increase the risk of serotonin toxicity and neuroleptic malignant syndrome (NMS) *moderate

Torsades de Pointes (TdP)[7]

- A polymorphic ventricular arrhythmia which can result in sudden cardiac death.
- Prolonged QTc interval on an EKG is an indicator of prolonged ventricular repolarization, which increases the risk of TdP and sudden cardiac death.
- For each 10 ms increase in QTc interval, there is a 5-7% increase in risk of developing TdP.
- QTc interval greater than 500 ms is considered very high risk of TdP and intervention is needed.

Non-drug risk factors for QT prolongation

- Hypokalemia
- hypomagnesemia
- hypocalcemia
- Bradycardia
- Structural heart disease, heart failure and MI
- Congenital long QT syndrome
- Female
- Advanced age

Drug Induced TdP

- Over 100 drugs available in Canada may cause QTc interval prolongation (only some are associated with TdP)
- Greater risk with IV administration of drugs.
- Often a greater risk at higher doses, or doses that are not appropriately adjusted for liver or kidney function.
- CYP450 interactions causing increased serum levels
- When therapy with QT prolonging drugs is necessary, ,use lowest effective dose, adjust for liver, kidney function and drug interactions.
- Onset of TdP after administration of QT prolonging drug is 72 hours (18%) 3-30 days (42%) after 30 days (40%)

Be aware of electrolyte depleting medications

- Potassium: agents with vomiting, diarrhea as side effect; high dose steroid
- Magnesium: PPIs (Mg absorption), cisplatin, carboplatin, aminoglycosides, cyclosporin, panitumumab, cetuximab
- Potassium/Magnesium: diuretics, amphotericin B
- Calcium: cisplatin, diuretics, bisphosphonates

Anticancer meds with possible TdP and major 3A4 substrates

- Bortezomib
- Bosutinib
- Ceritinib
- Crizotinib
- Dabrafenib
- Dasatinib
- Lapatinib
- Nilotinib
- Pazopanib
- Sunitinib
- Tamoxifen
- Toremifene
- Vemurafenib

*most new oral chemo are CYP3A substrates

Role of the Pharmacist in Reducing Risk of TdP

- When therapy with two or more QTc prolonging drugs is required, pharmacists can help reduce risk by ensuring[8]:
  - Electrolyte balance is maintained
  - Avoiding or mitigating drug interactions
  - Ensure appropriate dose adjustment of renally eliminated QTc prolonging drugs if kidney disease

Case 2: Risk of Torsades de Pointes

- Olanzapine is rated as conditional risk of TdP (only when taken in excessive doses, in the presence of electrolyte disturbances, interacting drugs etc.)
- Venlafaxine is rated as possible risk (can cause QT prolongation but no evidence of TdP when taken in usual doses)
- Ondansetron is rated as known risk (can cause QT prolongation with evidence of TdP even when taken in usual doses.)
  - No documented reports of TdP after a single, oral dose of ondansetron.

Case 2

- Risk of QT prolongation is significant due to long duration of ondansetron and three drugs with additive effect.
- Other than female sex, no other non-drug risk factors for TdP.

✓ Recommend decreasing ondansetron to pre-chemo and up to 24 hours after chemo

✓ Recommend baseline EKG if continuous use of ondansetron

✓ Recommend regular electrolyte monitoring

Case 2

- Potential serotonin toxicity and additive risk of neuroleptic malignant syndrome – do we have other options?

✓ Recommend discontinuing metoclopramide and use prochloperazine for prn anti-emetic

✓ Ask patient to monitor for symptoms of NMS such as fever, confusion, muscle rigidity

QT Resources

https://www.crediblemeds.org/oncosupport/

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