Let's Interact – A Discussion on Managing Drug Interactions in Oncology

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Presenter Disclosure

- **Faculty:** Kristi Hofer

- **Relationships with commercial interests:**
  - **Grants/Research Support:** none
  - **Speakers Bureau/Honoraria:** Amgen
  - **Consulting Fees:** none
  - **Other:** Employee of CancerCare Manitoba

Mitigating Potential Bias

- Have acted as a moderator at Amgen sponsored educational activity.
- Honorarium was forwarded to an education fund at CCMB, over which I have no signing authority.

Presenter Disclosure

- **Faculty:** Pat Trozzo

- **Relationships with commercial interests:**
  - **Grants/Research Support:** Unrestricted educational grant provided to pharmacy department from Hoffmann-LaRoche
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** None
  - **Other:** None

Mitigating Potential Bias

- Funds are overseen by a committee of pharmacists and pharmacy assistants. Decision to fund education or research rests with the committee.

Objectives

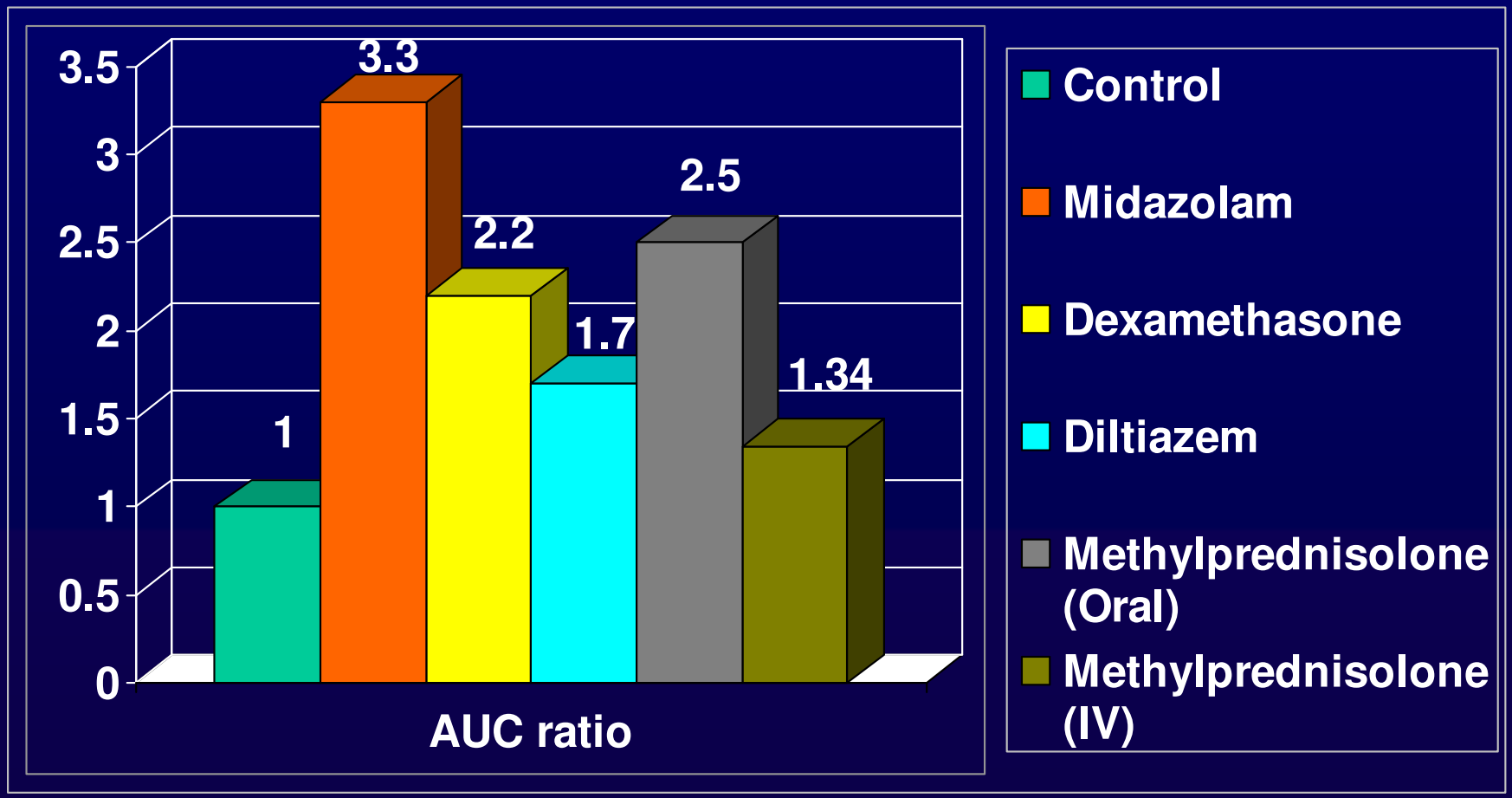
- Recommend appropriate management strategies for common drug interactions with supportive care drugs in oncology patients.
- Describe the process that CCMB pharmacists use to assess and communicate drug interactions for CCP patients.
- Explain the role of the CCP pharmacist in managing drug interactions throughout the course of a patient's treatment.

Interactions between the constituents of our systemic therapy regimens

Aprepitant and Dexamethasone

- Aprepitant is metabolized by the P450 isoenzyme CYP2C9. Additionally, it can inhibit the same isoenzyme affecting the metabolism of other drugs such as dexamethasone.
- *In vitro* data demonstrates that the serum levels of dexamethasone can be doubled by the addition of aprepitant.

Effect of Aprepitant on CYP3A4 Drugs



Aprepitant and Dexamethasone

- The initial clinical trials using aprepitant as additional antiemetic therapy used a dexamethasone dose of 20 mg.
- CancerCare Manitoba has predominantly used a dose of 12 mg as part of the antiemetic regimen for moderate and highly emetogenic systemic therapy.
- As such a dose reduction was not felt to be necessary when aprepitant was added.
- Dose reduction if experiencing dexamethasone side effects: insomnia, mania, blood sugars etc.

Leucovorin and Fluorouracil

- Leucovorin increases the activity of fluorouracil by stabilizing the complex of fluorouracil and thymidylate synthase.
- Important to keep in mind that this synergistic interaction can be a concern if patient is experiencing significant toxicity.
- School of thought that if dose reducing the fluorouracil, one should also reduce the leucovorin.

Sequence or Schedule Dependancy of Systemic agents

Paclitaxel and Carboplatin

- An advantageous sequence-dependant pharamacodynamic interaction occurs which results in decreased levels of thrombocytopenia when paclitaxel is infused prior to carboplatin.
- Proposed mechanism:
  - Paclitaxel effect on tubulin in platelets
  - Paclitaxel may spare megakaryocyte colony-forming units

Trastuzumab and Anthracyclines

- Concurrent administration of trastuzumab and doxorubicin (or epirubicin) increases the risk of cardiac toxicities in breast cancer patients.
- Initial trials added trastuzumab to combination of doxorubicin and paclitaxel in metastatic breast cancer resulting in cardiac dysfuction
  - 27% (with trastuzumab) vs 7% (without)
  - Class III/IV NYHA dysfunction 16% vs 3%

Interactions with patient medications that may affect therapy

Interactions with Irinotecan

- Irinotecan is extensively used in the treatment of metastatic colorectal cancer and lung cancer.
- Prodrug that is converted to the active metabolite, SN-38.
- The area under the curve (AUC) of SN-38 can be decreased by up to 42% during concomitant administration of St. John's wort.
- Phenytoin can reduce the AUC of irinotecan and SN-38 by 40% and 25% respectively.

Ondansetron

- *The lower dose intravenous regimen of 0.15 mg/kg every 4 hours for three doses may be used in adults with chemotherapy-induced nausea and vomiting. However, no single intravenous dose of ondansetron should exceed 16 mg due to the risk of QT prolongation*. US FDA June 29 2012
- *A single IV dose greater than 16 mg should not be given due to the dose dependent risk of QTc prolongation. The QTc prolongation effect of ONDANSETRON INJECTION is also expected to be greater if the drug is administered rapidly*. Health Canada product monograph Dec 12 2015
- Please contact me if you would like a copy of the power point presentation from Mark Friesen on the potential for Torsade de pointe with oncology agents.

Tamoxifen and Selective Serotonin Reuptake inhibitors (SSRIs)

- Specifically, strong CYP2D6 inhibitors may decrease the metabolic formation of highly potent active metabolites of tamoxifen. (Severity Major/ Reliability Rating Good)
- Researchers in California examined 16 887 breast cancer survivors (TNM stages 0-II) diagnosed between 1996 and 2007 and treated with tamoxifen in two California health plans.
- Author's conclusions: absolute subsequent breast cancer rates were similar among women who used paroxetine concomitantly with tamoxifen vs tamoxifen-only users. For the other antidepressants, we again found no such associations.

Haque R. J Natl Cancer Inst 2016 108(3)

Ibrutinib

- New daily oral medication for the treatment of chronic lymphocytic leukemia.
- Daily dose of 420 mg daily. Metabolized by CYP3A – will be affected by 3A inhibitors
- Strong inhibitors: clarithromycin, itraconazole
- Moderate inhibitors: ciprofloxacin, aprepitant, voriconazole, erythromycin
- Strong: withhold ibrutinib
- Moderate: reduce ibrutinib dose

Take home messages

- Need to look at potential interactions associated with components of our regimens when assessing side effects
- Consider what home medications the patient is taking and how they will affect the systemic therapy
- Consider the possibility of holding therapy with one of the interacting agents if that is clinically appropriate

Assessing Interactions: A Work in Progress

- Timing of Best Possible Medication History entry to ARIA is a challenge
- Lack of confidence in ARIA interaction alerts
  - Compare with Micromedex, Lexi-Comp
  - Food/alcohol interactions alert as 'life threatening'
- Pharmacist clinical judgment required
  - Leads to varied practice among pharmacists
- Interactions between existing home meds
  - ?scope

CCMB Policy: Responsibilities of Pharmacists

- Pharmacists must perform ARIA® interaction screening on all Cycle 1 chemotherapy orders
- Pharmacists will contact physicians when they encounter an interaction that they deem concerning for the patient. They will then document this intervention in the ARIA® progress notes.

CCMB Policy: Responsibilities of Pharmacists(2)

- Pharmacists who encounter or are notified of serious interactions will notify the patient of the interaction, expected results and mitigation strategies when it is clinically appropriate to involve the patient. The pharmacist shall document this interaction and notify the physician of the discussion with the patient.

CCMB Policy: Responsibilities of Nursing Staff

- Nurses encountering drug interactions with severity levels of 3 or 4 or drug-allergy interactions upon entering new medications must notify the physician and document that this has occurred in the ARIA® progress notes.

Survey of Pharmacist Practice (1)

- Source of med history
  - Primarily notes and DPIN
- Source of drug interaction information
  - 50% of pharmacists are also checking Micromedex or Lexi-comp in addition to the “screen” button in ARIA
- 70% of pharmacists stated that they were ‘somewhat comfortable’ assessing drug interactions

Survey of Pharmacist Practice (2)

- Discussion with pharmacists about varied practice:
  - Lack of consistent documentation in ARIA
  - General feeling that BPMH documented in the Med Hx tab in ARIA (completed at time of new patient visit) was either incomplete or not done in a timely manner (i.e. not inputted before Rx are written)
  - Lack of confidence in interaction database results in ARIA

The Process Going Forward

- Needs to be sustainable
- Needs to be within pharmacist scope
- Should not delay treatment or delay the orders being sent to CCP
- Should be consistent whether patient is treated at CCMB, WRHA or CCP

Proposed Approach

- Review Med Hx tab for BPMH
  - If not available; consult DPIN (+/- notes)
- Screen using ARIA 'screen' button
  - ? +/- additional check in Micromedex or Lexi-Comp
- Document relevant level 3-4 interactions in an ARIA progress note along with recommendation
  - Exclude interactions between existing home meds
  - Exclude mild/moderate interactions
  - Exclude food/drug interactions (addressed by patient counselling)
- Notify original prescriber of interaction
- Send orders to CCP

If the physician is responsible for acting on the recommendation and documenting the outcome…

Limitation	Benefit
Planned action/outcome may not be documented in a timely manner	No delay in sending orders to CCP
CCP staff may have to "search out" outcome/planned action	Within pharmacist scope (can't order EKG, change Rx)
CCP staff may have to facilitate prescription changes	

CCP Pharmacist Role

- Counsel patients on drug-food interactions
- ?Review/investigate the action taken by prescribing oncologist
  - Ensure team is aware of any changes to prescriptions or extra monitoring required
  - If none, bring to attention of CCP FPO
- When new drugs are started during active treatment, interactions reviewed at that time

Discussion

- CCP pharmacist response?
- Other team members?