Understanding Oncology Drug Interactions
Katie P. Morgan, PharmD, BCOP, CPP
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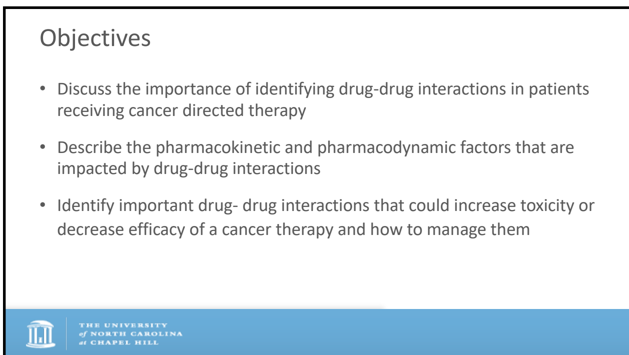
Katherine.morgan@unchealth.unc.edu


Objectives
• Discuss the importance of identifying drug-drug interactions in patients receiving cancer directed therapy
• Describe the pharmacokinetic and pharmacodynamic factors that are impacted by drug-drug interactions
• Identify important drug- drug interactions that could increase toxicity or decrease efficacy of a cancer therapy and how to manage them
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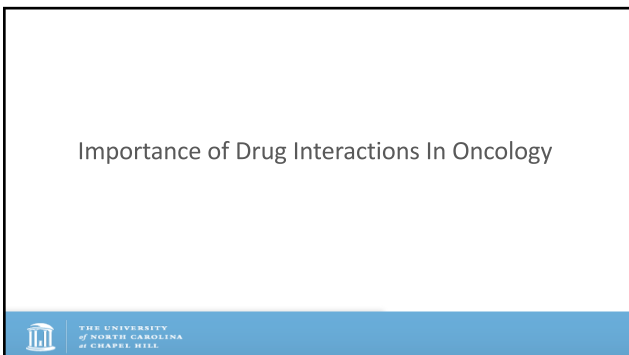
Importance of Drug Interactions In Oncology
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Importance of drug interactions to the health care professional

- Increased awareness of drug interactions allows providers to reduce risk of toxicity or ineffective treatment by choosing appropriate therapy and monitor for signs and symptoms of interactions

Blower P, et al. Crit Rev Oncol Hematol 2005; 55: 117-142.

Prevalence of DDI

- At least one potential drug-drug interaction found in 27-58% of ambulatory cancer patients
- At least one potential severe drug interaction involving chemotherapy found in 14% of patients ≥70 years old
- At least one potential drug-drug interaction in 46% of patients receiving oral anticancer drugs
- Drug-drug interactions estimated to be cause of approximately 4% of deaths

Popa MA, et al. J Geriatr Oncol 2014; http://dx.doi.org/10.1016/j.jgo.2014.04.002.
Van Leeuwen RW, et al. Br J Cancer 2013; 108: 1071-1078.

Current Trends

- FDA estimates that >25% of antineoplastic agents in pipeline now are planned as oral drugs
- Chronic daily dosing of oral chemotherapies
- Chronic disease state = Long-term cancer treatment
- Longer survival time = Increased medications for treatment of comorbidities

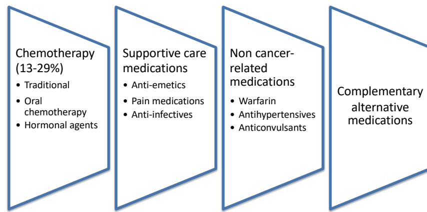
Weingart SN, et al. J Natl Compr Canc Netw 2008;6(supp3):S1-S14.
Riechelmann RP, et al. J Natl Cancer Inst 2007; 99: 592-600.

Cost of Drug interactions

- Morbidity and mortality due to drugs costs $136 billion per year
- Drug interactions represents 3-5% of in-hospital medication errors
- Drug interactions may contribute to 20-30% of adverse drug reactions
- Drug-drug interactions associated with longer length and increased cost of hospitalization (OR 4.38 and 1.79, respectively)

Preventable Adverse Drug Reactions: A Focus on Drug Interactions. Available at: www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm110632.htm
Kohler GI, et al. Int J Clin Pharmacol Ther 2000;38:504-513.
Moura C, et al. J Pharm Pharmaceut Sci 2009;12:266-272.

Medications Involved



Popa MA, et al. J Geriatr Oncol 2014; http://dx.doi.org/10.1016/j.jgo.2014.04.002
Riechelmann RP, et al. J Natl Cancer Inst 2007; 99: 592-600.
Riechelmann R et al. J Res Pharm Pract. 2016;5(2):77-78.

Risk Factors for Drug Interactions

- Number of drugs
  - Each additional medication (OR 1.4; P<0.0001)
  - Use of ≥8 drugs associated with potential drug interaction (P=0.0004)
- Use of over the counter drugs (OR 0.56; P=0.045)
- Type of medication (vs. supportive care meds only)
  - Drugs for comorbid conditions only (OR 8.6; P<0.0001)

Riechelmann RP, et al. Cancer Chemother Pharmacol 2005;56:286–290.
Riechelmann RP, et al. J Natl Cancer Inst 2007; 99: 592-600.
Van Leeuwen RW, et al. Ann Oncol 2011; 22:2334-2341.

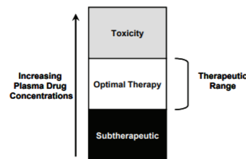
Drug interactions in cancer patients

- Major cause of morbidity and mortality
- High risk for drug interactions
- Multiple medications
  - Cytotoxic drugs with narrow therapeutic index
  - Hormonal agents
  - Supportive care medications
  - Medications for co-morbid conditions

Blower P, et al. Crit Rev Oncol Hematol 2005; 55: 117-142.

Effects of Drug interactions

- Increased toxicity
- Decreased therapeutic effect
- Combined Effect due to drug combination



Persky, AM, Foundations in Pharmacokinetics, 2017 (self-published text)

DDI Case 1

- JM is a 58 yo male who presents to clinic with newly diagnosed metastatic prostate cancer planning to start on abiraterone and prednisone.
  - PMH- hypertension, diabetes and osteoporosis
  - Home meds- ASA 81 mg daily, rosuvastatin 20 mg qHS, lisinopril 20 mg daily, diltiazem ER 360 mg daily, hydrochlorotiazide 25 mg daily, metformin 1000 mg BID, glyburide 3 mg daily, Oscal w/Vit D twice daily, tylenol 500 mg every 6 hours as needed
  - Labs- WNL

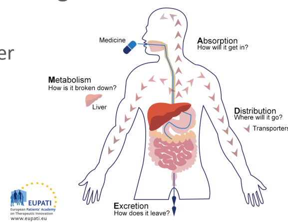
DDI Case 1- POLL

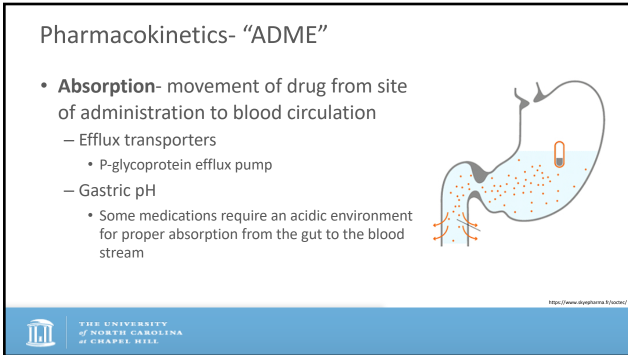
- Which one of the following increases JM's risk of drug interactions?
  A. Diagnosis
  B. Age
  C. Number of medications
  D. Number of comorbidities
  E. All of the above

Pharmacokinetic and Pharmacodynamic Factors Involved in Drug Interactions

Pharmacokinetic "ADME" Drug interactions

- How one drug affects another
  - Absorption
  - Distribution
  - Metabolism
  - Excretion





Dasatinib and Acid Suppression

- pH-dependent solubility
- Randomized, 3-treatment, crossover study in healthy patients
- Compared to dasatinib alone
  - No difference in exposure when antacid given 2 hours before dasatinib
  - Dasatinib exposure reduced by ~60% when famotidine given 10 hours before dasatinib
- Recommendations
  - H2 receptor antagonists and proton pump inhibitors (PPIs) should not be given with dasatinib
  - Antacids may be given if doses are separated from dasatinib by 2 hours

Eley T, et al. J Clin Pharmacol 2009;49:700-709.

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DDI Case 2

- SC is a 67 yo female diagnosed with CML she takes dasatinib 100 mg per day, she presents to clinic for follow up and tells you she has been having burning in her esophagus especially when laying down. Her friend says that omeprazole helped her indigestion so she started over the counter omeprazole last week and she feels much better.
  - PMH- osteopenia, asthma
  - Home Meds- cholecalciferol 1000 units daily, budesonide-formoteril 160-4.5 mcg/act 2 puff daily, albuterol 90 mg 2 puffs every 6 hours as needed
  - Labs
    - CBC- WBC 7.7, HGB 10.7, PLTS 296
    - BMP- Na 142, K 4.7, BUN 25, SCr 1.3, Gluc 109, Ca 9.0, Mg 2.0

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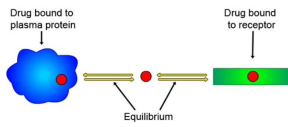
DDI Case 2-POLL

- How would you advise SC about her current self care for indigestion
  A. Continue omeprazole 20 mg daily and ensure she is taking it at 6 am
  B. Discontinue omeprazole, this could decrease the absorption of dasatinib and potentially decrease her ability to get to a major molecular response, recommend tums as needed not taken within 2 hours of dasatinib
  C. Discontinue omeprazole this could decrease the absorption of dasatinib and potentially decrease her ability to get to a major molecular response, recommend famotidine 20 mg BID
  D. Discontinue omeprazole, this could increase the absorption of dasatinib and cause hematologic toxicity, recommend tums as needed not taken within 2 hours of dasatinib

Pharmacokinetics- "ADME"

- **Distribution**- process of transferring from blood circulation to target tissues
  - Protein binding displacement
  - Tissue distribution



https://www.labce.com/spg570469_protein_binding.aspx

Paclitaxel and Warfarin

- Paclitaxel is 95-98% protein bound and Warfarin is 99% protein bound
- After administration of paclitaxel, warfarin can be displaced from protein binding sites
- Causes an increase in free warfarin concentration resulting in an increase in INR
- Monitoring of warfarin is required

Thompson ME, Highley MS. Interaction between paclitaxel and warfarin. Annals of Oncol 2003:14(500).

Pharmacokinetics- “ADME”

- **Metabolism**- conversion of drugs into compounds that are easier to eliminate
  - Phase I
    - CYP450 enzymes
  - Phase II

https://www.cyprotex.com/admepk/polymorphic-and-non-cyp-mediated-metabolism

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Cytochrome P450 Enzymes

- Enzymes involved in synthesis and breakdown of numerous molecules and chemicals
- CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 responsible for estimated >90% of drug oxidation
- CYP3A4
  - Metabolizes ~50% of drugs
  - Primarily in liver, but presence in small intestines plays important role in first-pass metabolism
- Induction typically seen several days to weeks after drug administration
- Inhibition seen immediately after drug administration

Blower P, et al. Crit Rev Oncol Hematol 2005; 55: 117-142.

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Cytochrome P450 Enzyme Inducers/Inhibitors

CYP450 Enzyme	Common Inhibitors	Common Inducers
3A4	Azole antifungals Diltiazem Verapamil Amiodarone Grapefruit Juice	Carbamazepine Phenytoin Rifampin Pioglitazone Dexamethasone
2C9	Amiodarone Fluconazole Metrolidazole	Carbamezapine Rifampin St. Johns Wart
2C19	PPIs Fluoxetine Isoniazid Oral Contraceptives	Rifampin Ritonavir St. Johns Wart
2D6	Fluoxetine Amiodarone Haloperidol Paroxetine Buproprion	

Ogu CC et al. Proc Bayl Univ Med Cent 2000;13(4):421-423.

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Vincristine and Azole Antifungals

- Vincristine metabolism mediated by CYP3A subfamily and substrate of P-glycoprotein (P-gp)
- Triazole antifungals inhibit CYP3A4
- Itraconazole and posaconazole also inhibit P-gp
- Increased adverse effects
  - Severe neurotoxicity (peripheral neuropathy)
  - Severe GI symptoms: constipation, ileus, abdominal pain/distension
  - Electrolyte abnormalities (hyponatremia and SIADH)
  - Seizures

Moriyama B, et al. Mycoses 2012;55:290-297.

Vincristine and Azole Antifungals

- Literature review and analysis of vincristine and azole antifungal case reports
- No case reports found for fluconazole
- Median time to adverse drug interaction with vincristine
  - Itraconazole: 9.5 days
  - Posaconazole 13.5 days
  - Voriconazole: 30 days
- Recommendations
  - Use alternative non-azole antifungal agent (i.e. echinocandins or liposomal amphotericin B)
  - Discontinue azole antifungal prior to vincristine administration

Moriyama B, et al. Mycoses 2012;55:290-297.

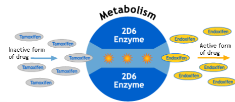
Enzalutamide is an CYP Enzyme Inducer

- Strong Inducer of CYP3A4, moderate inducer of CYP2C19 and CYP2C9
- A decrease in exposure with co-administration
  - 86% for 3A4 substrate midazolam
  - 70% for 2C19 substrate omeprazole
  - 56% for 2C9 substrate S-warfarin
- Recommendation
  - Drug therapy should be changed if possible to remove drug interactions as they would be ineffective in the setting of enzalutamide therapy

Benoist et al. Clin Pharmacokinet 2016;55:1369-1380

Tamoxifen and SSRI's

- Endoxifen is the active metabolite of tamoxifen which requires CYP2D6 for conversion
- Fluoxetine/Paroxetine inhibit CYP2D6
- Plasma concentrations of endoxifen statistically significantly decreased when co-administered with paroxetine
  - Mean of 12.4 ng/mL to 5.5 ng/mL after administration (P =.004)



Stearns et al. J Natl Cancer Inst 2003;95:1758-64.
http://services.dnadirect.com/grc/patient-site/tamoxifen-response/tamoxifen-and-some-antidepressants-dont-mix.html

DDI Case 3

- BB is a 39 yo with new diagnosis B cell ALL. She is being treated with CALGB 10403 which includes daunorubicin, vincristine peg-aspargase and prednisone. She has evidence of an aspergillosis lung infection and needs antifungal therapy. The plan is to discontinue fluconazole and start posaconaozle.
  - Current meds- levofloxacin 500 mg daily, pantoprazole 20 mg daily, sertraline 50 mg daily, valacyclovir 500 mg daily, fluconazole 400 mg daily, ondansetron 8 mg prn, prochlorperazine prn
  - Labs
    - CBC- WBC 15.3, HGB 7.1, HCT 20.2, PLTS 16, ANC 0.3
    - BMP- NA 138, K 4.1, Cl 102, SCr 0.96, BUN 18, Glu 106

DDI Case 3- POLL

- How would you manage BB's vincristine posaconazole drug interaction?
  A. Continue with recommendation to start posaconazole and monitor closely for toxicity
  B. Recommend to use an alternative fungal agent as posaconazole inhibits CYP3A4 and could cause life threatening toxicity due to increased exposure of vincristine
  C. Recommend to use an alternative fungal agent as posaconazole induces CYP2C9 which would cause decreased efficacy of vincristine leading to treatment failure
  D. Dose reduce vincristine to limit the toxicity associated with the drug interaction
  E. Discontinue vincristine since posaconazole is needed to treat aspergillosis

Pharmacokinetics- “ADME”

- **Excretion**- elimination of drug or metabolite from the body
  - Change in glomerular filtration
  - Altered renal tubular reabsorption
  - Changes in renal tubular secretion
  - Hepatotoxic/renal toxic effects of concomitant drug

High Dose Methotrexate and NSAIDs

- Methotrexate (MTX) is primarily eliminated by renal tubular secretion
- Co-administration of NSAIDs
  - inhibits tubular secretion of methotrexate
  - reduces renal blood flow to the kidneys by inhibiting prostaglandin synthesis
- Results in prolonged methotrexate serum concentrations
  - Increased risk of toxicity including hematologic
- Recommendations
  - Discontinue NSAIDs prior to MTX infusion and AVOID use of NSAIDs with methotrexate

Blower P, et al. Crit Rev Oncol Hematol 2005; 55: 117-142.

High Dose Methotrexate and PPIs

- Proposed Mechanism
  - PPI inhibition of renal H+/K+ -ATPase decreases active tubular secretion of methotrexate
  - Inhibition of breast cancer resistance protein (BCRP) involved in methotrexate transport
- Increased toxicity due to prolonged methotrexate clearance
  - Myelosuppression
  - Mucositis
  - Nephrotoxicity
- Discontinue PPI several days prior to administration of MTX

Blower P, et al. Crit Rev Oncol Hematol 2005; 55: 117-142.
Bezabeh S, et al. Oncologist 2012;17:550-554.

Other Important High Dose MTX Interactions

- Sulfonamides (Bactrim)
  - Bone marrow toxicity
  - Displacement of MTX from protein binding, inhibition of renal tubular secretion, additive antifolate effects
  - Avoid concomitant use, discontinue Bactrim at least 24 hours prior to administration
- Penicillins
  - Lead to increased MTX levels due to interference with MTX renal tubual secretion
  - Toxicity reported with amoxicillin, dicloxicllin, piperacillin, and many others
  - Avoid concomitant use or monitor MTX levels closely

Blower P, et al. Crit Rev Oncol Hematol 2005; 55: 117-142.

Pharmacodynamic Drug Interactions

- How the drugs affects the body
- Mechanism of action of multiple drugs influence the same physiological process
- Can be additive, synergistic, or antagonistic

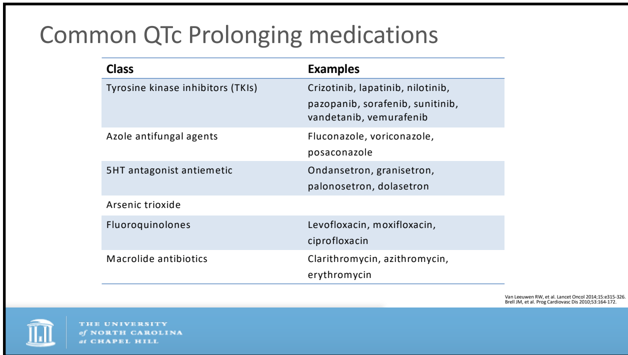
Pharmacodynamic Interaction	Incidence (%)
CNS Interactions	73%
GI Interactions	8%
QT Prolongation	4%
Other	15%

Van Leeuwen RW, et al. Br J Cancer 2013;108:1071-1078.
Blower P, et al. Crit Rev Oncol Hematol 2005;55:117-142.

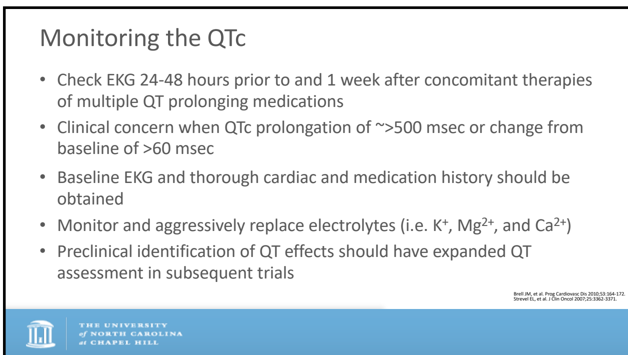
QT Prolongation- Additive Toxicity

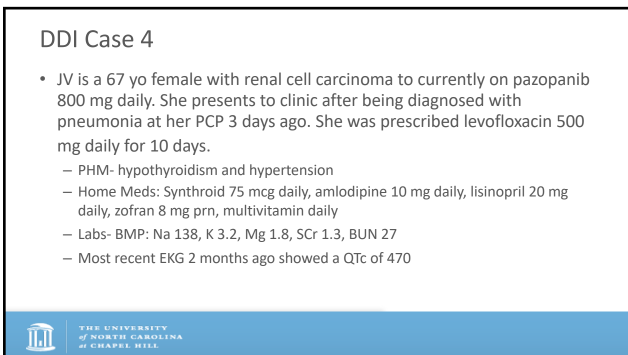
- Torsade de pointes (TdP) more likely to occur with:
  - QTc > 500 msec
  - Long intervals of prolongation
- Incidence of TdP: range from <1 in 10,000 to 1 in 100,000 cases
- Considerations in oncology patients
  - Prolonged QTc interval at baseline
  - General risk factors: older age, underlying coronary disease, previous myocardial infarction
  - Cancer-related risk factors: altered drug clearance, low electrolyte levels, multiple offending medications

Van Leeuwen RW, et al. Lancet Oncol 2014;15:e315-326.
Brell JM, et al. Prog Cardiovasc Dis 2010;53:164-172.



Class	Examples
Tyrosine kinase inhibitors (TKIs)	Crizotinib, lapatinib, nilotinib, pazopanib, sorafenib, sunitinib, vandetanib, vemurafenib
Azole antifungal agents	Fluconazole, voriconazole, posaconazole
5HT antagonist antiemetic	Ondansetron, granisetron, palonosetron, dolasetron
Arsenic trioxide	
Fluoroquinolones	Levofloxacin, moxifloxacin, ciprofloxacin
Macrolide antibiotics	Clarithromycin, azithromycin, erythromycin





DDI Case 4-POLL

- An EKG is preformed in the clinic the QTc is 505
- How would you manage JV's QTc prolongation at this time?
  - A. Discontinue levofloxacin and provide alternate therapy to treat pneumonia
  - B. Instruct the patient to stop using zofran and provide alternate therapy for nausea
  - C. Replace potassium, having low potassium increases your risk of torsade de pointes
  - D. A and B
  - E. All of the above

A Quick Note About Herbal Supplements

Chemotherapy- Herb Interactions

- Few clinical studies are conducted to evaluate herbal effects on drugs
- Herbs can affect PK and PD of chemotherapies
- Mechanisms of herbs and side effect reports are used to predict interactions and potential compounded toxicity
- Unregulated, unpredictable effects on chemotherapy, uncertain side effect profile

Liu B et al. Cancer Res 2005;65:879-886
Lawenda BD et al.J Natl Cancer Inst 2008;100:773-783

Examples Chemotherapy- Herb Interactions

- Phytoestrogens (herbal compounds mimics estradiol)
  - May stimulate growth of breast cancer cells and decrease the effectiveness of tamoxifen
  - Ginseng, dong quai, and red clover have phytoestrogen effects
  - Avoid in hormone sensitive cancers
- Antioxidants
  - Anthracyclines, platinum compounds, alkylating agents and bleomycin create reactive oxygen species for cytotoxic effects
  - Compounds considered to have antioxidant properties (i.e. grape seed, pine bark extracts, and tumeric) should be avoided

Liu B et al. Cancer Res 2005;65:879-886
Lawenda BD et al.J Natl Cancer Inst 2008;100:773-783

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Preventing Drug Interactions

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Strategies to Prevent DDI

- Drug interaction alerts at point of Computerized Physician Order Entry (CPOE)
- Drug interaction alerts upon pharmacist verification
- Admission medication reconciliation
- Discharge medication reconciliation
- Adverse event reporting (i.e. FDA MedWatch)
- Screening high risk patients

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Alert Fatigue

- Frequent “false” alarms or warnings that may not be clinically significant
- Institute for Safe Medication Practices (ISMP) recommendations
  - Reduce sensitivity of alert system
  - Identify conditions that lead to the most serious adverse events
  - Report invalid or clinical insignificant warnings
  - Generate report of bypassed alerts

ISMP. Heed this warning! Don’t miss important computer alerts. Available at: https://www.ismp.org/newsletters/acutecare/articles/20070208.asp

Drug Interactions in Oncology

- Drug interactions are important to recognize due to the narrow therapeutic index of cancer therapies which could lead to decreased efficacy or increased toxicity.
- Pharmacokinetics and pharmacodynamics for cancer drugs are important to understand when assessing drug interactions
- Management of drug interactions include close monitoring, choosing an alternate therapy or avoidance of a drug or drug class all together.