

Drug-drug Interactions between Oral Chemotherapy Agents and Drugs Commonly Dispensed in Community Pharmacy

Overview:

Oral chemotherapy drugs can be involved in significant drug-drug interactions (DDIs). Other members of the healthcare team may be unaware of DDIs making community pharmacists poised to intercept. Although most community pharmacies do not dispense chemotherapy drugs, documenting the use of these agents is important for identifying and managing DDIs. This newsletter will illustrate three common DDI scenarios involving oral chemotherapy agents:

- *the co-prescription of tamoxifen with antidepressants*
- *the co-prescription of tyrosine kinase inhibitors (“ib” drugs) with acid-reducing medications*
- *the use of androgen deprivation therapies with QT prolonging agents provide*

Introduction:

There has been a significant increase in the number of oral cancer chemotherapy agents developed and the use of these agents in recent years.¹ The oral route of administration benefits oncology patients because of increased convenience, improved quality of life, less interference with work/social life, avoidance of painful injections and prolonged infusion times, as well as offering ownership over their therapy.¹ However, with these benefits also come challenges associated with adherence and the increased potential for DDIs. An oncology patient’s drug therapy typically involves multiple medications including chemotherapy, hormonal agents, or supportive therapy.² Additionally, about 80 % of cancer patients have other comorbid conditions, such as cardiovascular, gastrointestinal, and rheumatological disease, which also require drug therapy.^{2,3} The risk of DDIs increases with the number of medications a patient takes concurrently, and as a result, they are common in oncology patients.^{2,3} Some chemotherapy agents have a fairly narrow therapeutic index, thus DDIs can result in significant negative outcomes, including therapeutic failure or toxicity.¹ It has been estimated that four percent of deaths in cancer patients are due to drug interactions.¹ A pharmacist must recognize significant interactions requiring intervention and be able to provide management strategies. The following are three common scenarios that may present when providing care to oncology patients.

Tamoxifen + Antidepressants:

Tamoxifen is an oral medication approved by Health Canada for treatment of breast cancer in women with hormone receptor positive tumours.⁴ It is extensively metabolized to active metabolites upon administration, and it is these metabolites that are likely the greatest contributors to tamoxifen’s efficacy.⁵ The most abundant metabolite, produced by

CYP 3A4, is N-desmethyl tamoxifen, which has comparable binding affinity to the parent drug. On the other hand, endoxifen, which is produced by CYP 2D6, has a much greater affinity for estrogen receptors and, therefore, is more potent. If CYP 2D6 activity is decreased, the conversion of tamoxifen into its active metabolites may also be decreased and negatively impact the success of tamoxifen treatment.

Antidepressants are commonly used to treat depression and/or vasomotor symptoms in women with breast cancer. Hot flashes, in particular, are a well-documented side effect of tamoxifen therapy and a common symptom experienced by menopausal women. After implementing appropriate lifestyle modifications, the first-line therapy to treat menopause-related vasomotor symptoms is hormone replacement therapy;⁶ however, this is contraindicated in breast cancer patients, thus the next option may be an antidepressant.⁶ Because many of the antidepressants inhibit CYP 2D6, the concern about compatibility with tamoxifen treatment is raised.⁷ Overall, studies to date have reported mixed findings, but there appears to be an emerging consensus that antidepressants which are moderate or strong inhibitors of CYP 2D6 should be avoided in combination with tamoxifen, while antidepressants which are mild or non-inhibitors are safer choices with less potential to decrease the efficacy of tamoxifen.⁷ A 2009 systematic review found consistent evidence that paroxetine and fluoxetine have major effects on the metabolism of tamoxifen, leading to a higher rate of breast cancer recurrence and mortality, and that bupropion is thought to have similar effects.⁷ Table 1 summarizes the antidepressants by potency of CYP 2D6 inhibition in order to assist the pharmacist in evaluating the significance of a tamoxifen-antidepressant DDI and to provide potential alternatives.

Table 1: Antidepressant potency of CYP 2D6 inhibition ⁷⁻⁹	
Strong	Bupropion Fluoxetine Paroxetine
Moderate	Duloxetine Sertraline*
Mild	Citalopram Escitalopram Fluvoxamine
Non-Inhibitors	Mirtazapine Venlafaxine Desvenlafaxine
*Breitbart, et al consider sertraline a strong inhibitor. ⁷	

Tyrosine Kinase Inhibitors + Acid-Reducing Drugs:

Tyrosine kinase inhibitors (TKIs) make up a large and expanding class of oral chemotherapy agents which are used for a variety of oncology indications.¹⁰ The suffix for most of these agents is “ib.” (e.g. dasatinib, elortinib) Many of the TKIs show pH-dependent solubility in the physiologically relevant pH range, which makes them potentially susceptible to DDIs when

co-administered with acid-reducing agents.¹¹ Because interactions involving CYP P450 enzymes may be more well-known, the importance of gastric acid-mediated DDIs may be overlooked.¹¹

GERD affects a large proportion of North Americans and cancer patients are no exception: acid-reducing agents are used in 20–33% patients undergoing cancer treatment.¹¹ In patients taking a TKI affected by pH, the combination with a proton-pump inhibitor (PPI), H₂ receptor antagonist (H₂RA), or antacid should be avoided.¹³ However, it is not always possible to completely avoid acid-reducing drugs; therefore the best management strategy is optimizing the timing of doses to minimize the effects of the interaction. A PPI may not be appropriate due to its prolonged effect on gastric pH and need for continuous dosing, thus even attempts at spacing doses are insufficient in avoiding DDIs.¹⁴ Pharmacists are poised to minimize GERD symptoms by counselling patients on lifestyle modifications.

Table 2 lists TKIs that are significantly affected by this interaction.¹³ The recommendations for managing pH mediated DDIs are listed in the specific TKI product monographs and should be consulted when determining management strategies.

Absorption significantly affected by acid-reducing drugs	May be administered with acid-reducing drugs
Crizotinib	Axitinib
Dasatinib	Imatinib
Erlotinib	Ruxolitinib
Gefitinib	Sorafenib
Lapatinib	Sunitinib
Nilotinib	Vandetanib
Pazopanib	Vemafenib

Androgen Deprivation Therapy + QT prolonging agents:

Torsades de pointes (TdP), or “twisting of the points” refers to a potentially fatal ventricular tachycardia associated with a prolonged QT interval and bradycardia.¹⁵ This arrhythmia may be a result of congenital long QT syndrome or an acquired state, usually due to the use of QT prolonging drugs.¹⁶ Other risk factors for developing TdP include: female sex, advanced age, electrolyte disturbances, cardiovascular disease, malnutrition, obesity, hypothyroidism, and polypharmacy.¹⁵ The exact incidence of long QT syndrome (LQTS) and TdP among cancer patients remains unknown however cancer patients may be particularly prone to QT prolongation. Up to 36% of cancer patients have registered baseline ECG abnormalities¹⁷ and have other risk factors for TdP, particularly polypharmacy. Although many drugs have a small effect on the QT interval, when used in combination the risk of significant consequences increases.

Androgens are protective against drug-induced prolongation of repolarization and testosterone has been implicated as the major factor lowering the risk of TdP in men.²⁰ Therefore androgen deprivation therapy, a commonly used treatment in prostate cancer, has the potential to contribute to QT prolongation.²⁰ When another QT prolonging agent is co-

administered, consideration of the patient’s overall risk of LQTS and TdP is important. Table 3 lists commonly used drugs in androgen deprivation therapy.²¹

Luteinizing hormone– releasing hormone (LHRH) agonists (by injection)	Leuprolide Goserelin Buserelin Triptorelin
LHRH antagonists (by injection)	Degarelix
Anti-androgens (orally administered)	Flutamide Bicalutamide Nilutamide Abiraterone Enzalutamide

Patients with risk factors for TdP must be individually assessed. A frequently updated reference, crediblemeds.org, contains information on drugs that prolong the QT interval by providing a risk category. If the DDI is unavoidable, the patient should be counselled on the signs of TdP (e.g. palpitations, syncope).²² For patients with major or multiple risk factors, a baseline ECG is recommended prior to initiating QT-prolonging drugs.¹⁹

Conclusion:

The expanding use of oral cancer treatments is making it increasingly likely that pharmacists will encounter DDIs among their oncology patients. These DDIs can potentially affect the therapeutic outcome or result in significant adverse effects. As such, the pharmacist plays an important role in managing these DDIs.

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