Managing Drug Interactions in Cancer Therapy: A Guide for the Advanced Practitioner

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CASE STUDY

Mrs. P is a 30-year-old woman who presented to our bone marrow transplant program with myelodysplastic syndrome (MDS). She received a haploidentical allogeneic stem cell transplant with a conditioning regimen consisting of busulfan and cyclophosphamide. This treatment was followed by post-transplant immunosuppression for graft-versus-host disease (GVHD) with cyclophosphamide, mycophenolate mofetil (MMF), and tacrolimus (see Table 1 for medication list). Tacrolimus levels were monitored twice a week with adjustment to a goal range of between 5 and 10 ng/mL. We initiated tacrolimus at a dose of 0.03 mg/kg by mouth twice daily (rounded to 2 mg by mouth twice daily). Drug interactions were assessed by the clinical pharmacist prior to admission, routinely with medication changes, and then upon discharge.

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Drug-interaction related risk factors include the use of drugs that are significantly impacted by inhibition or induction of drug metabolism (tyrosine kinase inhibitors [TKIs]), the use of drugs that have a significant inhibitory or inducing capacity of drug metabolism (certain antifungal medications), and the use of drugs with a narrow therapeutic window such as warfarin. Patient-specific risk factors include older age, renal or hepatic dysfunction, hematologic cancers, and the use of many prescribed medications (Panesar, 2011).

One retrospective drug review in cancer patients showed a high frequency of drug interactions. A total of 278 patients were reviewed, of which 40% of patients had reported potential drug interactions with their chemotherapy (van Leeuwen et al., 2011). Although this shows a high risk of drug interactions in cancer patients, it is unknown from this study what percentage of interactions were clinically relevant. In this article, we will introduce concepts and use clin-

Table 1. Medication List for Case Study Patient

Conditioning chemotherapy	Busulfan: 0.8 mg/kg/dose IV × 16 doses days –8 to –4 Cyclophosphamide: 50 mg/kg/dose × 2 doses days –3 and –2
Immunosuppression regimen for GVHD	Cyclophosphamide: 50 mg/kg/dose × 2 doses days +3 and +4 Tacrolimus: 0.03 mg/kg/dose po bid (2 mg po bid) starting day +5 Mycophenolate mofetil: 1,000 mg po every 8 hours days +5 to +35
Antibiotic prophylaxis	Ciprofloxacin: 500 mg po bid starting day +1 Penicillin VK: 500 mg po bid starting day +1 Posaconazole: 300 mg po daily starting day +5 Acyclovir: 400 mg po bid starting day +1
Additional medications	Pantoprazole: 40 mg po daily Sucralfate: 1 g po tid Levetiracetam: 500 mg po bid day –8 to –3 for seizure prevention with busulfan Fosaprepitant: 150 mg IV days –8, –3, and +3 Ondansetron: 8 mg IV bid days –8 to +5 Lorazepam: 1 mg IV every 6 hours prn for nausea/vomiting Ursodiol: 600 mg po bid

Note. IV = intravenous; GVHD = graft-versus-host-disease; po = by mouth; bid = twice daily; tid = three times daily; prn = as needed.

ically relevant examples to highlight the risk of drug interactions in patients with cancer.

Drug-drug interactions are common, not only in the oncology setting but also in the older adult population, and may be responsible for up to 4% of deaths in hospitalized oncology patients (Buajordet, Ebbesen, Erikssen, Brors, & Hilberg, 2001). A study by Van Leeuwen and associates (2013) noted that more than half of ambulatory patients with cancer had at least one potential drug interaction. One-third of ambulatory patients with cancer had a major potential drug interaction that could result in serious clinical consequences.

Identified risk factors for drug interactions are listed in Table 2. One universal identified risk factor is an age-related change, including changes in the gastrointestinal tract (increased or decreased absorption), decreases in body fat that may influence the length of time a drug remains in the body, and decreased hepatic and renal function. A study by Popa and colleagues (2014) examined records of 244 patients who were 70+ years of age and undergoing chemotherapy. This study found 75% of patients receiving chemotherapy had a potential for a serious drug interaction involving chemotherapeutic agents.

Other risk factors include polypharmacy, defined as the use of more medications than often medically required, and the increasing number of doses of a medication per day (Cope, 2013; Planton & Edlund, 2010; Popa et al., 2014; van Leeuwen et al., 2011). As many as 80% of oncology patients utilize over-the-counter medications (Van Leeuwen et al., 2011), and these agents are not often recorded in the patient's medical record. Patients with cancer are at a higher risk due to the increasing number of daily medications—both oncologic drug(s) as well as supportive medications.

Many new agents approved for the treatment of cancer are orally administered, indicating they are under the influence of pharmacokinetic drug interactions including absorption, distribution, metabolism, and excretion (ADME), which can reduce their effectiveness or increase toxicity. In fact, 60% of new agents approved for cancer treatment by the US Food and Drug Administration (FDA) between 2012 and 2014 were orally administered (FDA, 2017a). Most of these drugs are significantly impacted by pharmacokinetic drug interactions.

In this article, we will focus on pharmacokinetic drug interactions, but it is important to understand that other types of drug interactions such as pharmacodynamic interactions may occur. Simply stated, a pharmacokinetic interaction is the effect of the body on the drug, and a pharmacodynamic interaction is the drug's effect on the body (Beijnen & Schellens, 2004). Pharmacodynamic drug interactions are actually very common, and such examples include the use of multiple central nervous systems (CNS) depressants or the combination of nonsteroidal anti-inflammatory drugs

(NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors.

PHARMACOKINETIC DRUG INTERACTIONS

Absorption

The absorption of various oral chemotherapy agents is often influenced by multiple factors such as food and acid-suppressive agents. Ultimately, these factors can impact the solubility and bioavailability of chemotherapy agents (Halfdanarson & Jatoi, 2010). For example, many oral TKIs are influenced by gastric pH changes, as seen in Tables 3 and 4. Specifically, Table 4 illustrates how the pH-dependent solubility of dasatinib (Sprycel) decreases as pH increases (Bristol-Myers Squibb, 2008; Eley et al., 2009).

There are ways to mitigate the impact of acid suppression on drug absorption. They include the use of H2 blockers at specific times around administration of the TKI, as described in Table 3. Another reported option is to use a beverage that decreases the stomach pH for a short period such as a cola beverage (van Leeuwen et al., 2016). Furthermore, food can significantly alter the absorption of chemotherapy agents; however, the effect of food is not consistent among all chemotherapy agents, as illustrated in Table 5 (Koch et al., 2009; Reigner et al., 1998).

Distribution

Specific drug characteristics such as high protein binding (> 90%), narrow therapeutic index, high hepatic extraction ratio, and intravenous dosage forms may increase the likelihood of altered distribution. In particular, the impact of plasma protein binding is often overemphasized in the literature and training (Rolan, 1994). For example, TKIs are highly protein bound, but there is minimal evidence of major interactions with drugs that have the ability to displace them from the protein-binding sites.

Table 2. Risk Factors for Drug Interactions

- Older age
- Polypharmacy
- Low body weight
- Renal insufficiency
- Hematologic cancer
- Six or more comorbidities
- Longer length of hospital stay
- History of adverse drug reactions
- Intake of highly protein-bound drugs
- Increasing number of prescribed medications

Note. Information from Cope (2013); Planton & Edlund (2010); Popa et al. (2014); van Leeuwen et al. (2011).

Metabolism

Metabolism primarily occurs in the liver involving cytochrome P450 enzymes. Multiple drugs (refer to Table 6) competitively inhibit or induce cytochrome P450 enzyme–binding sites. This can alter the metabolism of oral and intravenous chemotherapy agents, ultimately influencing their efficacy and safety (Guengerich, 2008; Zanger & Schwab, 2013).

For example, as illustrated in Table 6, antifungals such as voriconazole, posaconazole, and ketoconazole are very strong cytochrome P450 3A4 inhibitors, which interact with a large majority of TKIs. Certain TKIs such as ibrutinib (Imbruvica) and everolimus (Afinitor) could have profound

Table 3. Impact of pH on Select Tyrosine Kinase Inhibitors[a]

TKI	Acid-suppressive agent	AUC change	Reference
Axitinib	Rabeprazole: 20 mg daily	↓ 15%	Budha (2012)
Erlotinib	Omeprazole: 40 mg daily	↓ 46%	Budha (2012)
Imatinib	Omeprazole: 40 mg daily	No change	Egorin (2009)
Lapatinib	Esomeprazole: 40 mg daily	↓ 27%	Glaxo Clinical Trial Report (2009)
Nilotinib	Esomeprazole: 40 mg daily	↓ 34%	Yin (2010)

Note. TKI = tyrosine kinase inhibitor; AUC = area under concentration-time curve.
[a]The US Food and Drug Administration does not require studies for drug approval; variable availability of published data.

Table 4. Dasatinib and Acid-Suppressive Agents

TKI	Acid-suppressive agent	AUC change
Dasatinib	Famotidine: 40 mg, 10 hours before dasatinib	↓ 61%
	Famotidine: 40 mg, 2 hours after dasatinib	No significant difference
	Aluminum hydroxide, magnesium hydroxide, simethicone: 30 mL, 2 hours before dasatinib	No significant difference
	Aluminum hydroxide: 30 mL, with dasatinib	↓ 55%
	Omeprazole: 40 mg daily	↓ 43%

Note. TKI = tyrosine kinase inhibitor; AUC = area under concentration-time curve. Information from Eley et al. (2009); Glaxo Clinical Trial Report (2009).

toxicity if administered with strong inhibitors of CYP 3A4 (Kovarik et al., 2005; de Jong et al., 2015). On the other hand, rifampin or other strong inducers of CYP3A4 could significantly decrease the activity of many of the TKIs, as shown in Table 7. For these reasons, we recommend careful assessment for drug interactions any time a patient starts treatment with TKIs.

Elimination

Elimination occurs mainly via the kidneys or bile. A small portion of chemotherapy agents such as methotrexate and cisplatin are primarily removed via elimination from the kidneys. High-dose methotrexate treatment can cause severe harm and even death in patients who have difficulty eliminating methotrexate and/or active metabolites of methotrexate. Certain drugs such as specific antibacterials, proton pump inhibitors, and NSAIDs can reduce the elimination of methotrexate (Ferreri et al., 2004; Fjeldborg, Sorensen, & Helkjaer, 1986; Hammor & Hasan, 2013).

PREVENTION AND MANAGEMENT STRATEGIES FOR ADVANCED PRACTITIONERS

All oncology advanced practitioners (AP) have a vital role in the prevention, early detection, and prompt management of drug-drug interactions. As the number of oral oncologic agents increases, more safety issues and adherence issues will abound. The first step in this process of prevention and early detection of any adverse drug reaction is a full medication and health history review. The patient is instructed to bring any medication—prescribed or over-the-counter—to his clinic visit. The drug names, dosages, and schedule are documented. Any herbal supplements and/or vitamins should be documented along with dosages. Specific vernacular may be utilized to address sociocultural diversities (e.g., words such as "natural" products, folk medicine, or "home remedies"; salves; creams; and potions; Ben-Arye, Halabi, Attias, Goldstein, & Schiff, 2014).

Medical records from other health-care providers should also be examined, including clinic notes, hospitalization records, and emergency department (ED) reports. It is also important to note any potential drug absorption issues due to previous surgeries, feeding tubes, or diseases such as Crohn's disease.

It is estimated that up to 90% of patients use some sort of alternative or complementary medicines or therapies (Arslan, Tural, & Akar, 2013; Mao, Palmer, Healy, Desai, & Amsterdam, 2011; Naing et al., 2011; Yates et al., 2005). Yet the ma-

Table 5. Impact of Food on the Absorption of Select Chemotherapy Agents

Oral chemotherapy agent	Impact of food	Proper administration
Capecitabine	↓ absorption	Take with water 30 minutes after food
Lapatinib	↑ absorption	Take on an empty stomach (1 hour before or 1 hour after food)

Note. Information from Koch et al. (2009); Reigner et al. (1998).

Table 6. Select Cytochrome P450 Inhibitors and Inducers

CYP enzymes	Strong inhibitors [≥ 5-fold increase in AUC or > 80% decrease in CL]	Moderate inhibitors [≥ 2 but < 5-fold increase in AUC or 50%–80% decrease in CL]	Weak inhibitors [≥ 1.25 but < 2-fold increase in AUC or 20%–50% decrease in CL]
CYP1A2	Ciprofloxacin, enoxacin, fluvoxamine	Methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, zileuton	Acyclovir, allopurinol, caffeine, cimetidine, daidzein, disulfiram, Echinacea, famotidine, norfloxacin, propafenone, propranolol, terbinafine, ticlopidine, verapamil
CYP2B6	–	–	Clopidogrel, ticlopidine prasugrel
CYP2C8	Gemfibrozil	–	Fluvoxamine, ketoconazole, trimethoprim
CYP2C9	–	Amiodarone, fluconazole, miconazole, oxandrolone	Capecitabine, cotrimoxazole, etravirine, fluvastatin, fluvoxamine, metronidazole, sulfinpyrazone, tigecycline, voriconazole, zafirlukast
CYP2C19	Fluconazole, fluvoxamine, ticlopidine	Esomeprazole, fluoxetine, moclobemide, omeprazole, voriconazole	Allicin (garlic derivative), armodafinil, carbamazepine, cimetidine, etravirine, human growth hormone (rhGH), felbamate, ketoconazole, oral contraceptives
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton
CYP2D6	Bupropion, fluoxetine, paroxetine, quinidine	Cinacalcet, duloxetine, terbinafine	Amiodarone, celecoxib, cimetidine, desvenlafaxine, diltiazem, diphenhydramine, Echinacea, escitalopram, febuxostat, gefitinib, hydralazine, hydroxychloroquine, imatinib, methadone, oral contraceptives, propafenone, ranitidine, ritonavir, sertraline, telithromycin, verapamil
CYP enzymes	**Strong inducers [≥ 80% decrease in AUC]**	**Moderate inducers [50%–80% decrease in AUC]**	**Weak inducers [20%–50% decrease in AUC]**
CYP1A2	–	Montelukast, phenytoin, smokers vs. nonsmokers	Moricizine, omeprazole, phenobarbital
CYP2B6	–	Efavirenz, rifampin	Nevirapine
CYP2C8	–	Rifampin	
CYP2C9	–	Carbamazepine, rifampin	Aprepitant, bosentan, phenobarbital, St. John's wort
CYP2C19	–	Rifampin	Artemisinin
CYP3A	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, Echinacea, pioglitazone, prednisone, rufinamide
CYP2D6	None known	None known	None known

Note. AUC = area under concentration-time curve; CL = clearance. Information from FDA (2017b).

Table 7. Select Tyrosine Kinase Inhibitor CYP3A4 Drug Interactions

TKI	Inducer	Inhibitor	AUC change (respectively)	Reference
Abiraterone acetate	Rifampin	Ketoconazole	↓ 42%/no change	Bernard (2015)
Axitinib	Rifampin	Ketoconazole	↓ 79%/↑ 106%	Pithavala (2010, 2012)
Cabozantinib	Rifampin	Ketoconazole	↓ 77%/↑ 38%	Nguyen (2015)
Crizotinib	Rifampin	Ketoconazole	↓ 82%/↑ 320%	Xu (2015)
Dasatinib	Rifampin	Ketoconazole	↓ 82%/↑ 256%	Johnson (2010)
Enzalutamide	Not studied	Itraconazole	–/↑ 130%	Gibbons (2015)
Erlotinib	Rifampin	Ketoconazole	↓ 67%/↑ 86%	Rakhit (2008)
Everolimus	Rifampin	Ketoconazole	↓ 63%/↑ 1,500%	Kovarik (2002, 2005)
Ibrutinib	Rifampin	Ketoconazole	↓ 89%/↑ 2,400%	de Jong (2015)
Imatinib	Rifampin	Ketoconazole	↓ 74%/↑ 40%	Bolton (2004); Dutreix (2004)
Ixazomib	Rifampin	Clarithromycin	↓ 74%/no change	Gupta (2015)
Lapatinib	Carbamazepine	Ketoconazole	↓ 72%/↑ 257%	Smith (2009)
Lenvatinib	Rifampin	Ketoconazole	↓ 18%/↑ 19%	Shumaker (2014, 2015)
Nilotinib	Rifampin	Ketoconazole	↓ 80%/↑ 201%	Tanaka (2011)
Palbociclib	Rifampin	Itraconazole	↓ 85%/↑ 87%	Hoffman (2015, 2016)
Pazopanib	Not studied	Ketoconazole	–/↑ 65%	Tan (2013)
Ponatinib	Rifampin	Ketoconazole	↓ 63%/↑ 78%	Narasimhan (2013, 2015)
Regorafenib	Rifampin	Ketoconazole	↓ 50%/↑ 33%	Bayer (2016)
Sorafenib	Rifampin	Ketoconazole	↓ 37%/no change	Lathia (2006)
Sunitinib	Rifampin	Ketoconazole	↓ 46%/↑ 51%	Adams & Leggas (2007)
Venetoclax	Rifampin	Ketoconazole	↓ 74%/↑ 640%	Salem (2016)

Note. TKI = tyrosine kinase inhibitor; AUC = area under concentration-time curve.

jority of these patients do not disclose this information to their health-care providers (Mao et al., 2011; Oh et al., 2010; Yates et al., 2005; Yildirim, 2010).

The FDA ensures the safety and efficacy of a drug released to the public. Nutritional products and supplements are exempt from this review process, however (Vogel, 2011). Patients do not understand this concept and often assume the lack of FDA regulation makes these products "safe." Unfortunately, ingredients in the products can be variable and unspecified, and there can be a lack of quality control—meaning there can be meaningful differences in the amounts of the product between different batches (Arslan et al., 2013). The AP must ensure patients understand the importance of disclosing any and all alternative/complementary therapies.

There are risk assessment tools to assist APs to prevent, monitor for, and/or allow early identification of symptoms (Table 8). These tools may prompt APs to prescribe an appropriate medication or prevent the prescription of an inappropriate prescription. Other tools can aid APs in evaluating a medication's potential effect on a patient's functional and disease status. Cope (2013) noted 10 essential assessment elements to evaluate medications in older adults (Table 9).

The AP risk assessment not only includes a thorough medication review, but also the documentation of any side effects experienced by a patient. Patients should be questioned about any previous adverse events from any therapy. Assessment for substance abuse is also important, as drug metabolism may be affected. For example, smoking can induce drug-metabolizing enzymes

Table 8. Risk Assessment Tools for Prescribing Appropriate Medications

Tool	Acronym	Comments
START	**S**creening **T**ool to **A**lert Doctors to **R**ight **T**reatment	• Organized by organ systems • To prevent omission of appropriate medication
STOPP	**S**creening **T**ool of **O**lder **P**erson's **P**otentially Inappropriate Prescriptions	• For identification of inappropriate prescription • Provides 65 criteria for potentially inappropriate prescribing in older adults
ARMOR	**A**ssess, **R**eview, **M**inimize, **O**ptimize, **R**eassess	• Systematic approach to evaluation medications • Considers function and disease status • Emphasizes quality of life and functional status maintenance

Note. Information from American Geriatrics Society (2012); Cope (2013); Haque (2009); Lam & Cheung (2012).

of cytochrome P450, thus decreasing the efficacy of some oncologic agents as well as other categories of drugs (O'Malley, King, Conte, Ellingrod, & Ramnath, 2014; Sohn et al., 2015). Subcutaneous medications may have suboptimal absorption due to smoking effects. The stimulatory effects of smoking could lessen the effects of drugs such as the benzodiazepines and opioids. If a patient should suddenly quit smoking, the practitioner must maintain alertness to the possibility of a drug overdose due to increased drug exposure, such as with methadone (Zevin & Benowitz, 1999).

Thorough patient education, including proper dosing and scheduling instructions, is imperative to decrease potential drug interactions. Written information as well as verbal instructions are needed. Reminder devices such as a smartphone or an alarm clock could be helpful. Pill boxes may be useful, but many oral oncologic agents should not be placed in pill boxes, but left in the original container protected from light and moisture (Drug Information Service, University of Utah Hospitals and Clinics, 2016). The prescribing information may be consulted for details about medication storage and handling.

Ideally, a drug-drug interaction is prevented. Up to 30% of adverse drug events in the outpatient setting are preventable (Gurwitz et al., 2003). Any prescription is carefully evaluated. Limiting the number of medications in older adults can reduce the risk of drug-drug interaction. Six or more medications increases the risk of an adverse drug event times four (Pretorius, Gataric, Swedlund, and Miller, 2013). Each new medication prescribed adds more than one adverse drug event a year. Multiple prescribers also increase adverse drug events; each additional prescriber increases the risk of an adverse drug event by 30% (Pretorius et al., 2013).

Every prescriber should share records and medication lists. Prescribers should avoid treating every side effect with another medication, considering if the dose of the offending medication could be decreased or changed to another medication (Pretorius et al., 2013). When a new medication is prescribed, a follow-up visit 2 to 4 weeks after initiating the medication is in order. In older adults, the Beers criteria should be observed (American Geriatrics Society, 2012).

The Beers criteria give a comprehensive list of medications to be avoided or used with caution in older adults. Drugs that are on this list include benzodiazepines, diphenhydramine, ibuprofen,

Table 9. Essential Elements of Medication Assessment in Older Adults

- Cognitive function
- Social support resources
- Review of the Beers criteria
- Assessment of nutritional status
- Review of potential drug interactions
- Assessment of activities of daily living
- Assessment of hepatic and renal function
- Financial resources and prescription coverage
- Evaluation of each medication's indications, benefits, and side effects
- Review of the patient's complete medication list, including prescription, over-the-counter medications, herbs, and supplements

Note. Information adapted from Cope (2013).

megestrol acetate, metoclopramide, promethazine, sliding-scale insulin, and zolpidem among others. Special attention should be given to those with a history of an adverse drug event, those who are nonadherent, those who have cognitive impairment or psychiatric disease, those who have substance abuse problems, and those who live alone.

Before increasing a dose of a medication due to seemingly suboptimal effect, APs must consider whether nonadherence is an issue. Any unnecessary medications should be discontinued. Recommended lab monitoring for certain medications should be followed according to the FDA prescribing information. When prescribing a medication, it is recommended to avoid starting more than one medication at a time (Pretorius et al., 2013).

Although prescribers and patients must be knowledgeable about potential drug adverse reactions, the office staff must also be educated about oral oncologic agents and drug-drug interactions. Telephone triage personnel must be educated about the signs of a potential drug interaction and promptly intervene if one is suspected. The medical oncology office staff should have an oral medication adherence assessment protocol and dedicated nursing staff for oral regimens (Moody & Jackowski, 2010). Clinical decision support systems may improve prescribing quality as well by alerting the prescriber to potential drug interactions or dosages that might be incorrect. However, APs should beware of "alert fatigue," which can occur when there is poor alert specificity (Seidling et al., 2014; Weingart, Zhu, Young-Hong, Vermilya, & Hassett, 2014).

The oncology AP should maintain a high index of suspicion for a drug-drug interaction. Some common signs of an adverse drug event might include a fall; orthostatic hypotension; heart failure; delirium or cognitive impairment; a change in daily functioning; a hospital admission; or exaggerated common adverse events (Pretorius et al., 2013). Notation should be made of the timing of symptoms after a new medication starts or after a dose change.

If a drug interaction is noted, the AP should evaluate the clinical significance of the event. The number of drugs involved should be noted. Options for management should then be reviewed and may include removal of the offending agent, removal of the affected agent, potential dose adjustments of medication, or prescription of an alternative agent(s).

CASE STUDY

Patients with leukemia are at a heightened risk of drug interactions due to the frequent use of medications that interact with cytochrome P450 enzymes, such as antifungal medications. Posaconazole, for example, is a broad-spectrum azole antifungal and a strong inhibitor of the CYP3A4 isoenzyme. Multiple medications the patient in our case study received were metabolized at least partially by CYP3A4, including cyclophosphamide and tacrolimus. Posaconazole was not initiated until day +5 after stem cell transplantation, to reduce the risk of a potential drug interaction with cyclophosphamide, which was administered on days –3, –2, +3, and +4. Although posaconazole has not been studied in combination with cyclophosphamide, itraconazole has been shown to increase levels of the potentially more toxic metabolites (Marr et al., 2004).

Tacrolimus is an immunosuppressant used to decrease the risk of graft-versus-host disease (GVHD), a common complication of stem cell transplantation. Tacrolimus is metabolized predominately by CYP3A4; therefore, dosing requirements are significantly decreased (> 50%) when it is used concomitantly with strong inhibitors of CYP3A4 (El-Dahshan, Bakr, Donia, Badr, & Sobh, 2004). It is important to monitor levels meticulously, as subtherapeutic levels may increase the risk of GVHD, whereas supratherapeutic levels may increase the risk of kidney dysfunction. Table 10 includes tacrolimus levels and doses throughout the inpatient admission and in the clinic.

Tacrolimus levels initially were subtherapeutic. Over time, however, the posaconazole decreased tacrolimus metabolism through inhibition of CYP3A4. The full impact of changes in cytochrome P450 enzyme activity and a clinical interaction may not be immediately apparent, due to a delay in hepatic enzyme inhibition caused by the posaconazole and a lag in the increase in tacrolimus drug levels. This example highlights the pharmacovigilance necessary and the role APs play in monitoring patients for critical drug interactions.

Table 10. Tacrolimus Adjustments due to Drug Interaction

Day	Tacrolimus dose	Trough tacrolimus level (ng/mL)
+5	Started tacrolimus at 2 mg po bid	–
+8	Increased to 2.5 mg po bid	3.8
+10	Continued 2.5 mg po bid	5.7
+13	Held 1 dose, decreased to 1.5 mg po bid	16.8
+16	Decreased to 1 mg po AM, 1.5 mg po at night	10.4
+19	Decreased to 1 mg po bid	11.2
+22	Continued 1 mg po bid	8.6

Note. po = by mouth; bid = twice daily.

Disclosure

The authors have no potential conflicts of interest to disclose.

References

Adams, V. R. & Leggas, M. (2007). Sunitinib malate for the treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumors. *Clinical Therapeutics, 29*(7), 1338–1353. https://doi.org/10.1016/j.clinthera.2007.07.022

American Geriatrics Society (AGS). (2012). American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society, 60*(4), 616–631. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22376048

Arslan, D., Tural, D., & Akar, E. (2013). Herbal administration and interaction of cancer treatment. *Journal of Palliative Medicine, 16*(11), 1466–1476. https://doi.org/10.1089/jpm.2013.0126

Bayer HealthCare Pharmaceuticals, Inc. (2016). Stivarga (regorafenib) package insert. Retrieved from http://labeling.bayerhealthcare.com/html/products/pi/Stivarga_PI.pdf

Beijnen, J. H., & Schellens, J. H. (2004). Drug interactions in oncology. *Lancet Oncology, 5*(8), 489–496. https://doi.org/10.1016/S1470-2045(04)01528-1

Ben-Arye, E., Halabi, I., Attias, S., Goldstein, L., & Schiff, E. (2014). Asking patients the right questions about herbal and dietary supplements: Cross cultural perspectives. *Complementary Therapies in Medicine*, 22(2), 304–310. https://doi.org/10.1016/j.ctim.2014.01.005

Bernard, A., Vaccaro, N., Acharya, M., Jiao, J., Monbaliu, J., De Vries, R.,...Chien, C. (2015). Impact on abiraterone pharmacokinetics and safety: Open-label drug-drug interaction studies with ketoconazole and rifampicin. *Clinical Pharmacology in Drug Development, 4*(1), 63–73. https://doi.org/10.1002/cpdd.132

Bolton, A. E., Peng, B., Hubert, M., Krebs-Brown, A., Capdeville, R., Keller, U., & Seiberling, M. (2004). Effect of rifampicin on the pharmacokinetics of imatinib mesylate (Gleevec, STI571) in healthy subjects. *Cancer Chemotherapy and Pharmacology, 53*(2), 102–106. https://doi.org/10.1007/s00280-003-0722-9

Bristol-Myers Squibb. (2008). The effect of omeprazole on the pharmacokinetics of dasatinib (BMS-354825) in healthy subjects. Retrieved from http://ctr.bms.com/pdf/CA180249.pdf

Buajordet, I., Ebbesen, J., Erikssen, J., Brors, O., & Hilberg, T. (2001). Fatal adverse drug events: The paradox of drug treatment. *Journal of Internal Medicine, 250*(4), 327–341. https://doi.org/10.1111/j.1365-2796.2001.00892.x

Budha, N. R., Frymoyer, A., Smelick, G. S., Jin, J. Y., Yago, M. R., Dresser, M. J.,...Ware, J. A. (2012). Drug absorption interactions between oral targeted anticancer agents and PPIs: Is pH-dependent solubility the Achilles heel of targeted therapy? *Clinical Pharmacology and Therapeutics, 92*(2), 203–213. https://doi.org/10.1038/clpt.2012.73

Cascorbi, I. (2012). Drug interactions—principles, examples and clinical consequences. *Deutsches* Ärzteblatt *International, 109*(33–34), 546–556. https://doi.org/10.3238/arztebl.2012.0546

Cope, D. (2013). Polypharmacy in older adults: The role of the advanced practitioner in oncology. *Journal of the Advanced Practitioner in Oncology, 4*(2), 107–112. https://doi.org/10.6004/jadpro.2013.4.2.5

de Jong, J., Skee, D., Murphy, J., Sukbuntherng, J., Hellemans, P., Smit, J.,...Mannaert, E. (2015). Effect of CYP3A perpetrators on ibrutinib exposure in healthy participants. *Pharmacology Research and Perspectives, 3*(4), e00156. https://doi.org/10.1002/prp2.156

Drug Information Service, University of Utah Hospitals and Clinics. (2016). Oral medications that should not be packaged in the prepackage machine and oral medications that require special handling precautions. Retrieved from http://www.ashp.org/DocLibrary/MemberCenter/SICP/Univ-of-Utah-do-not-prepack-list.pdf

Dutreix, C., Peng, B., Mehring, G., Hayes, M., Capdeville, R., Pokorny, R., & Seiberling, M. (2004). Pharmacokinetic interaction between ketoconazole and imatinib mesylate (Gleevec) in healthy subjects. *Cancer Chemotherapy and Pharmacology, 54*(4), 290–294. https://doi.org/10.1007/s00280-004-0832-z

Egorin, M. J., Shah, D. D., Christner, S. M., Yerk, M. A., Komazec, K. A., Appleman, L.R.,...Beumer, J. H. (2009). Effect of a proton pump inhibitor on the pharmacokinetics of imatinib. *British Journal of Clinical Pharmacology, 68*(3), 370–374. https://doi.org/10.1111/j.1365-2125.2009.03466.x

El-Dahshan, K. F., Bakr, M. A., Donia, A. F., Badr, A. E., & Sobh, M. A. (2004). Co-administration of ketoconazole to tacrolimus-treated kidney transplant recipients: A pro-

spective randomized study. *Nephrology Dialysis Transplantation, 19*(6), 1613–1617. https://doi.org/10.1093/ndt/gfh191

Eley, T., Luo, F. R., Agrawal, S., Sanil, A., Manning, J., Li, T.,... Bertz, R. (2009). Phase I study of the effect of gastric acid pH modulators on the bioavailability of oral dasatinib in healthy subjects. *Journal of Clinical Pharmacology, 49*(6), 700–709. https://doi.org/10.1177/0091270009333854

Ferreri, A. J., Guerra, E., Regazzi, M., Pasini, F., Ambrosetti, A., Pivnik, A.,...Reni, M. (2004). Area under the curve of methotrexate and creatinine clearance are outcome-determining factors in primary CNS lymphomas. *British Journal of Cancer, 90*(2), 353–358. https://doi.org/10.1038/sj.bjc.6601472

Fjeldborg, P., Sorensen, J., & Helkjaer, P. (1986). The long-term effect of cisplatin on renal function. *Cancer, 58*(10), 2214–2217. https://doi.org/10.1002/1097-0142(19861115)58:10<2214::AID-CNCR2820581009>3.0.CO;2-I

Gibbons, J. A., de Vries, M., Krauwinkel, W., Ohtsu, Y., Noukens, J., van der Walt, J. S.,...Ouatas, T. (2015). Pharmacokinetic drug interactions studies with enzalutamide. *Clinical Pharmacokinetics, 54*(10), 1057–1069. https://doi.org/10.1007/s40262-015-0283-1

Glaxo Clinical Trial Report. (2009). An open-label, single sequence study to examine the effects of esomeprazole on the pharmacokinetics of orally administered lapatinib in subjects with metastatic ErbB2 positive breast cancer. Retrieved from http://www.gsk-clinicalstudyregister.com/files2/9ed5ea0d-8365-439f-98e4-96119b2189e9

Guengerich, F. P. (2008). Cytochrome P450 and chemical toxicology. *Chemical Research in Toxicology, 21*(1), 70–83. https://doi.org/10.1021/tx700079z

Gupta, N., Hanley, M., Venkatakrishnan, K., Bessudo, A., Sharma, S., O'Neil, B.,...Nemunaitis, J. (2015). Abstract B147: A phase 1 drug-drug interaction study between ixazomib, an oral proteasome inhibitor, and rifampin in patients with advanced solid tumors. *Molecular Cancer Therapeutics, 14*(12 suppl 2). https://doi.org/10.1158/1535-7163.TARG-15-B147

Gurwitz, J. H., Field, T. S., Harrold, L. R., Rothschild, J., Debellis, K., Seger, A. C.,...Bates, D. W. (2003). Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA, 289*(9), 1107–1116. https://doi.org/10.1001/jama.289.9.1107

Halfdanarson, T. R., & Jatoi, A. (2010). Oral cancer chemotherapy: The critical interplay between patient education and patient safety. *Current Oncology Reports, 12*(4), 247–252. https://doi.org/10.1007/s11912-010-0103-6

Hammor, Y. A., & Hasan, Y. (2013). Prevention and management of high-dose methotrexate toxicity. *Journal of Cancer Science and Therapy, 5*, 106–112. http://dx.doi.org/10.4172/1948-5956.1000193

Haque, R. (2009). ARMOR: A tool to evaluate polypharmacy in elderly persons. *Annals of Long-Term Care, 17*(6), 26–30. Retrieved from http://www.managedhealthcareconnect.com/content/armor-a-tool-evaluate-polypharmacy-elderly-persons

Hoffman, J. T., Loi, C. M., O'Gorman, M., Plotka, A., Kosa, M., Jakubowska, A., & Wang, D. D. (2016). Abstract LB-196: A phase I open-label, fixed-sequence, two-period crossover study of the effect of multiple doses of itraconazole on palbociclib (PD–0332991) pharmacokinetics in healthy volunteers. *Cancer Research, 76*(14 suppl). https://doi.org/10.1158/1538-7445.AM2016-LB-196

Hoffman, J. T., Plotka, A., O'Gorman, M., Chang, A., Kosa, M., Loi, C.,...Wang, D. D. (2015). Abstract 4515: A phase 1 randomized, open-label, fixed-sequence, 2-period study of the effect of multiple doses of rifampin on palbociclib (PD-0332991) pharmacokinetics in healthy volunteers. *Cancer Research, 75*(15 suppl). https://doi.org/10.1158/1538-7445.AM2015-4515

Johnson, F. M., Agrawal, S., Burris, H., Rosen, L., Dhillon, N., Hong, D.,...Chiappori, A. A. (2010). Phase 1 pharmacokinetic and drug-interaction study of dasatinib in patients with advanced solid tumors. *Cancer, 116*(6), 1582–1591. https://doi.org/10.1002/cncr.24927

Koch, K. M., Reddy, N. J., Cohen, R. B., Lewis, N. L., Whitehead, B., Mackay, K.,...Lewis, D. D. (2009). Effects of food on the relative bioavailability of lapatinib in cancer patients. *Journal of Clinical Oncology, 27*(8), 1191–1196. https://doi.org/10.1200/JCO.2008.18.3285

Kovarik, J. M., Beyer, D., Bizot, M. N., Jiang, Q., Shenouda, M., & Schmouder, R. L. (2005). Blood concentrations of everolimus are markedly increased by ketoconazole. *Journal of Clinical Pharmacology, 45*(5), 514–518. https://doi.org/10.1177/0091270005275368

Kovarik, J. M., Hartmann, S., Figueiredo, J., Rouilly, M., Port, A., & Rordorf, C. (2002). Effect of rifampin on apparent clearance of everolimus. *Annals of Pharmacotherapy, 36*(6), 981–985. https://doi.org/10.1345/aph.1A384

Lam, M. P., & Cheung, B. M. (2012). The use of STOPP/START criteria as a screening tool for assessing the appropriateness of medications in the elderly population. *Expert Review of Clinical Pharmacology, 5*(2), 187–197. http://dx.doi.org/10.1586/ecp.12.6

Lathia, C., Lettieri, J., Cihon, F., Gallentine, M., Radtke, M., & Sundaresan, P. (2006). Lack of effect of ketoconazole-mediated CYP3A inhibition on sorafenib clinical pharmacokinetics. *Cancer Chemotherapy and Pharmacology, 57*(5), 685–692. https://doi.org/10.1007/s00280-005-0068-6

Mao, J. J., Palmer, C. S., Healy, K. E., Desai, K., & Amsterdam, J. (2011). Complementary and alternative medicine use among cancer survivors: A population-based study. *Journal of Cancer Survivorship, 5*(1), 8–17. http://dx.doi.org/10.1007/s11764-010-0153-7

Marr, K. A., Leisenring, W., Crippa, F., Slattery, J. T., Corey, L., Boeckh, M., & Mcdonaold, G. B. (2004). Cyclophosphamide metabolism is affected by azole antifungals. *Blood, 103*(4), 1557–1559. https://doi.org/10.1182/blood-2003-07-2512

Moody, M. & Jackowski, J. (2010). Are patients on oral chemotherapy in your practice setting safe? *Clinical Journal of Oncology Nursing, 14*(3), 339–346. https://doi.org/10.1188/10.CJON.339-346

Naing, A., Stephen, S. K., Frenkel, M., Chandhasin, C., Hong, D. S., Lei, X.,...Kurzrock, R. (2011). Prevalence of complementary medicine use in a phase 1 clinical trials program: The MD Anderson Cancer Center Experience. *Cancer, 117*(22), 5142–5150. http://dx.doi.org/10.1002/cncr.26164

Narasimhan, N. I., Dorer, D. J., Davis, J., Turner, C. D., & Sonnichsen, D. (2015). Evaluation of the effect of multiple doses of rifampin on the pharmacokinetics and safety of ponatinib in healthy subjects. *Clinical Pharmacology in Drug Development, 4*(5), 354–360. https://doi.org/10.1002/cpdd.182

Narasimhan, N. I., Dorer, D. J., Niland, K., Haluska, F., & Son-

nichsen, D. (2013). Effects of ketoconazole on the pharmacokinetics of ponatinib in healthy subjects. *Journal of Clinical Pharmacology, 53*(9), 974–981. https://doi.org/10.1002/jcph.109

Nguyen, L., Holland, J., Miles, D., Engel, C., Benrimoh, N., O'Reilly, T., & Lacy, S. (2015). Pharmacokinetic (PK) drug interaction studies of cabozantinib: Effect of CYP3A inducer rifampin and inhibitor ketoconazole on cabozantinib plasma PK and effect of cabozantinib on CYP2C8 probe substrate rosiglitazone plasma PK. *Journal of Clinical Pharmacology, 55*(9), 1012–1023. https://doi.org/10.1002/jcph.510

O'Malley, M., King, A., Conte, M., Ellingrod, V., & Ramnath, N. (2014). Effects of cigarette smoking on metabolism and effectiveness of systemic therapy for lung cancer. *Journal of Thoracic Oncology, 9*(7), 917–926. https://doi.org/10.1097/JTO.0000000000000191

Oh, B., Butow, P., Mullan, B., Clarke, S., Tattersall, M., Boyer, M.,...Larke, L. (2010). Patient-doctor communication: Use of complementary and alternative medicine by adult patients with cancer. *Journal of the Society for Integrative Oncology, 8*(2), 56–64. https://www.ncbi.nlm.nih.gov/pubmed/20388446

Panesar, K. A. (2011). Typical drug interactions in oncology. *US Pharmacist, 36*(1 oncology suppl), 7–9. Retrieved from http://www.uspharmacist.com/content/s/153/c/26151

Pithavala Y. K., Tong, W., Mount, J., Rahavendran, S. V., Garrett, M., Hee, B.,...Klamerus, K. J. (2012). Effect of ketoconazole on the pharmacokinetics of axitinib in healthy volunteers. *Investigational New Drugs, 30*(1), 273–281. https://doi.org/10.1007/s10637-010-9511-6

Pithavala, Y. K., Tortorici, M., Toh, M., Garrett, M., Hee, B., Kuruganti, U.,...Klamerus, K. J. (2010). Effect of rifampin on the pharmacokinetics of axitinib (AG-013736) in Japanese and Caucasian healthy volunteers. *Cancer Chemotherapy and Pharmacology, 65*(3), 563–570. https://doi.org/10.1007/s00280-009-1065-y

Planton, J., & Edlund, B. (2010). Strategies for reducing polypharmacy in older adults. *Journal of Gerontology Nursing, 36*(1), 8–12. https://doi.org/10.3928/00989134-20091204-03

Popa, M., Wallace, K., Brunello, A., Extermann, M., & Balducci, L. (2014). Potential drug interactions and chemotoxicity in older patients with cancer receiving chemotherapy. *Journal of Geriatric Oncology, 5*(3), 307–314. https://doi.org/10.1016/j.jgo.2014.04.002

Pretorius, R. W., Gataric, G., Swedlund, S. K., & Miller, J. R. (2013). Reducing the risk of adverse drug events in older adults. *American Family Physician, 87*(5), 331–336. Retrieved from http://www.aafp.org/afp/2013/0301/p331.html

Rakhit, A., Pantze, M. P., Fettner, S., Jones, H. M., Charoin, J. E., Riek, M.,...Hamilton, M. (2008). The effects of CYP3A4 inhibition on erlotinib pharmacokinetics: Computer-based simulation (SimCYP) predicts in vivo metabolic inhibition. *European Journal of Clinical Pharmacology, 64*(1), 31–41. https://doi.org/10.1007/s00228-007-0396-z

Reigner, B., Verweij, J., Dirix, L., Cassidy, J., Twelves, C., Allman, D.,...Osterwalder, B. (1998). Effect of food on the pharmacokinetics of capecitabine and its metabolites following oral administration in cancer patients. *Clinical Cancer Research, 4*(4), 941–948.

Rolan, P. E. (1994). Plasma protein binding displacement interactions—Why are they still regarded as clinically important? *British Journal of Clinical Pharmacology, 37*(2), 125–128. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1364588/

Salem, A., Agarwal, S., Dunbar, M., Enschede, S. L., Humerickhouse, R. A., & Wong, S. L. (2016). Pharmacokinetics of venetoclax, a novel BCL-2 inhibitor, in patients with relapsed or refractory chronic lymphocytic leukemia or non-Hodgkin's lymphoma. *Journal of Clinical Pharmacology, 57*(4), 484–492. https://doi.org/10.1002/jcph.821

Seidling, H., Klein, U., Schaier, M., Czock, D., Theile, D., Pruszydlo, M.,...Haefeli, W. E. (2014). What if all alerts were specific: Estimating the potential impact on drug interaction alert burden. *International Journal of Medical Informatics, 83*(4), 285–291. https://doi.org/10.1016/j.ijmedinf.2013.12.006

Shumaker, R., Jagadeesh, A., Fan, J., Martinez, G., Thompson, G. A., & Ren, M. (2014). Effect of rifampicin on the pharmacokinetics of lenvatinib in healthy adults. *Clinical Drug Investigation, 34*(9), 651–659. https://doi.org/10.1007/s40261-014-0217-y

Shumaker, R., Jagadeesh, A., Fan, J., Martinez, J., Thompson, G. A., & Ren, M. (2015). Effects of ketoconazole on the pharmacokinetics of lenvatinib (E7080) in healthy participants. *Clinical Pharmacology in Drug Development, 4*(2), 155–160. https://dx.doi.org/10.1002%2Fcpdd.140

Smith, D. A., Koch, K. M., Arya, N., Bowen, C. J., Herendeen, J. M., & Beelen, A. (2009). Effects of ketoconazole and carbamazepine on lapatinib pharmacokinetics in healthy subjects. *British Journal of Clinical Pharmacology, 67*(4), 421–426. https://doi.org/10.1111/j.1365-2125.2009.03370.x

Sohn, H., Kim, H., Song, I., Lim, E., Kwon, M., Ha, J., & Kwon, J. (2015). Evidence supporting the need for considering the effects of smoking on drug disposition and effectiveness in medication practices: A systematic narrative review. *International Journal of Clinical Pharmacology and Therapeutics, 53*(8), 621–634. https://doi.org/10.5414/CP202260

Tan, A. R., Gibbon, D. G., Stein, M. N., Lindquist, D., Edenfield, J. W., Martin, J. C.,...Stephenson, J. J. (2013). Effects of ketoconazole and esomeprazole on the pharmacokinetics of pazopanib in patients with solid tumors. *Cancer Chemotherapy and Pharmacology, 71*(6), 1635–1643. https://doi.org/10.1007/s00280-013-2164-3

Tanaka, C., Yin, O. Q., Smith, T., Sethuraman, V., Grouss, K., Galitz, L.,...Schran, H. (2011). Effects of rifampin and ketoconazole on the pharmacokinetics of nilotinib in healthy participants. *Journal of Clinical Pharmacology, 51*(1), 75–83. https://doi.org/10.1177/0091270010367428

US Food and Drug Administration. (2017b). FDA drug development and drug interactions: Table of substrates, inhibitors and inducers. Retrieved from http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

US Food and Drug Administration. (2017a). Hematology/oncology (cancer) approvals and safety notifications. Retrieved from http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

Van Leeuwen, R., Brundel, D., Neef, C., van Gelder, T., Mathijssen, R., Burger, D., & Jansman, F. (2013). Prevalence of potential drug-drug interactions in cancer patients treated with oral anticancer drugs. *British Journal of Cancer,*

108, 1071–1078. https://doi.org/10.1038/bjc.2013.48

Van Leeuwen, R., Peric, R., Hussaarts, K., Kienhuis, E., Ijzerman, N. S., de Bruin, P.,...Mathijssen, R. H. (2016). Influence of the acidic beverage cola on the absorption of erlotinib in patients with non–small-cell lung cancer. *Journal of Clinical Oncology, 34*(12), 1309–1314. https://doi.org/10.1200/JCO.2015.65.2560

Van Leeuwen, R., Swart, E., Boven, E., Boom, F., Schuitenmaker, M., & Hugtenburg, J. (2011). Potential drug interactions in cancer therapy: A prevalence study using an advanced screening method. *Annals of Oncology, 22*(10), 2334–2341. https://doi.org/10.1093/annonc/mdq761

Vogel, W. (2011). Internet oncology: Cure seekers beware! *Journal of the Advanced Practitioner in Oncology, 2*(6), 409–412. https://doi.org/10.6004/jadpro.2011.2.6.9

Weingart, S., Zhu, J. Young-Hong, J., Vermilya, H., & Hassett, M. (2014). Do drug interaction alerts between a chemotherapy order-entry system and an electronic medical record affect clinician behavior? *Journal of Oncology Pharmacy Practice, 20*(3), 163–171. https://doi.org/10.1177/1078155213487395

Xu, H., O'Gorman, M., Tan, W., Brega, N., & Bello, A. (2015). The effects of ketoconazole and rifampin on the single-dose pharmacokinetics of crizotinib in healthy subjects. *European Journal of Clinical Pharmacology, 71*(12), 1441–1449. https://doi.org/10.1007/s00228-015-1945-5

Yates, J. S., Mustian, K. M., Morrow, G. R., Gillies, L. J., Padmanaban, D., Atkins, J. N.,...Colman, L. K. (2005). Prevalence of complementary and alternative medicine use in cancer patients during treatment. *Supportive Care in Cancer, 13*(10), 806–811. http://dx.doi.org/10.1007/s00520-004-0770-7

Yildirim, Y. (2010). Patterns of the use of complementary and alternative medicine in women with metastatic cancer. *Cancer Nursing, 33*(3), 194–200. http://dx.doi.org/10.1097/NCC.0b013e3181c295ac

Yin, O. Q., Gallagher, N., Fischer, D., Demirhan, E., Zhou, W., Golor, G., & Schran, H. (2010). Effect of the proton pump inhibitor esomeprazole on the oral absorption and pharmacokinetics of nilotinib. *Journal of Clinical Pharmacology, 50*(8), 960–967. https://doi.org/10.1177/0091270009346061

Zanger, U. M., & Schwab, M. (2013). Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacology and Therapeutics, 138*(1), 103–141. https://doi.org/10.1016/j.pharmthera.2012.12.007

Zevin, S., & Benowitz, N. (1999). Drug interactions with tobacco smoking: An update. *Clinical Pharmacokinetics, 36*(6), 425–438. https://doi.org/10.2165/00003088-199936060-00004