ORAL CHEMOTHERAPY: NEW FRONTIERS FOR ONCOLOGY DIETITIANS

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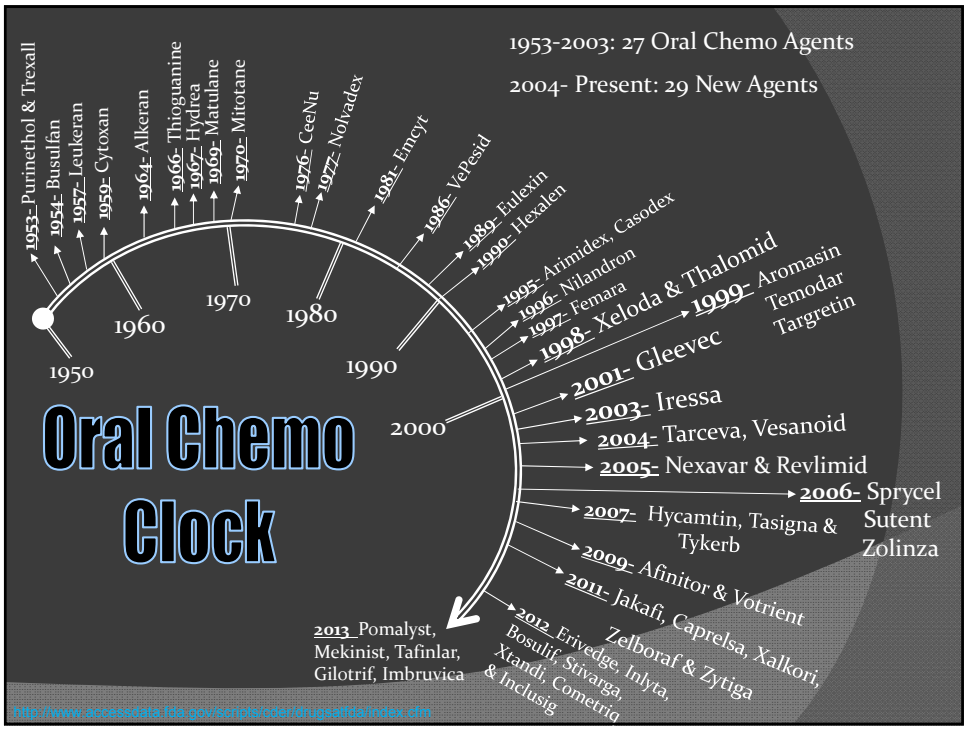
Objectives

- Become familiar with currently available oral agents used to treat cancer
- Indentify important drug-food interactions that occur with oral oncolytics
- Explain how oncology dietitians can improve patient care by consulting on patients utilizing oral oncolytics

Outline

- Review currently available oral agents on the market
- Describe common drug-food interactions and management issues
- Review the "grapefruit" issue and effects on medication metabolism
- Discuss the acid suppression therapy issues with specific oral agents
- Describe issues with supplements, vitamins and minerals specific to oral agents



Management Issues with OC

- Adherence/Compliance
- Work Flow
- Accessibility
- Food & Drug Interactions
- Side-Effects
  - Can be severe, not observed in clinic
- Perceived Lack of Efficacy
- Costs

Question

- Which of the following pharmacokinetic parameters is most affected by food-drug interactions
  - A) Absorption
  - B) Distribution
  - C) Metabolism
  - D) Excretion
  - E) Tastiness

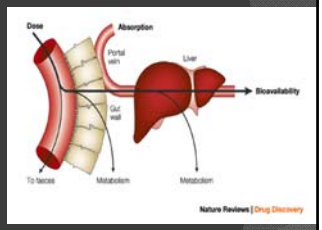
Mechanisms of Interaction

- Altering Absorption of Drugs
  - Food can decrease rate or extent of drug absorption
    - Slows intestinal transport
    - Reduces solubility of drug formulations
    - High fiber can bind certain drugs
  - Food can enhance absorption of drugs
    - Mainly seen with lipid soluble drugs
  - Chelation between divalent/trivalent cations can reduce absorption of drugs
    - Ca, Mg, Al, Fe, Zn
  - Altering gastric pH

Pronsky & Crowe. Food Medication Interactions. © 2013
Won CS, et al. Pharmacology & Therapeutics. 2012

Mechanisms of Interaction

- Altering Distribution of Drugs
  - Many drugs bind albumin during circulation
  - Only free drug has an effect on the body
  - Edema = third spacing= hypoalbuminemia
    - Ex. Phenytoin, warfarin, etc
- Altering Metabolism of Drugs
  - Foods can alter liver metabolism of drugs
    - See Grapefruit section
- Altering Excretion of Drugs
  - Nutrients can alter renal excretion of drugs
    - Ex. High sodium intake competes with drugs like lithium



Pronsky & Crowe. Food Medication Interactions. © 2013
Won CS, et al. Pharmacology & Therapeutics. 2012

Absorption Effects w/OC

- 56 oral agents available
  - 9 taken with food
  - 19 taken on an empty stomach
- 2 supportive care medications also have absorption issues
  - Deferasirox (Exjade) – variable absorption with food
  - Eltrombopag (Promacta) – Calcium chelation

Segal E, Flood M, Mancini R et al. Publication pending.

Absorption Effects w/OC

Take with Food	Take on an empty stomach
Altretamine (Hexalen)	Abiraterone (Zytiga)
Bexarotene (Targretin)	Afatinib (Gilotrif)
Bosutinib (Bosulif)	Cabozantinib (Cometriq)
Capecitabine (Xeloda)	Chlorambucil (Leukeran)
Cyclophosphamide (Cytoxan)	Dabrafenib (Tafinlar)
Exemestane (Aromasin)	Deferasirox (Exjade)*
Imatinib (Gleevec)	Eltrombopag (Promacta)*
Regorafenib (Stivarga)	Erlotinib (Tarceva)
Vorinostat (Zolinza)	Estramustine (Emcyt)
	Ibrutinib (Imbruvica)**
	Lapatinib (Tykerb)
	Lomustine (CeeNu)
	Melphalan (Alkeran)
	Mercaptopurine (Purinethol)
	Nilotinib (Tasigna)
	Pazopanib (Votrient)
	Pomalidomide (Pomalyst)
	Sorafenib (Nexavar)
	Temozolomide (Temodar)
	Thalidomide (Thalomid)
	Trametinib (Mekinist)

*Supportive care medications typically used in cancer care

**Although PI doesn't specifically recommend taking on empty stomach, AUC can be doubled if taken with food.

Segal E, Flood M, Mancini R et al. J Oncol Practice. Epub ahead of print.

OC with Food

- Capecitabine (Xeloda)
  - Food delays time to peak plasma level 90 minutes and reduced peak concentration 60%
  - Manufacturer recommends with food as that was the study design
  - Recommendations
    - How much food is enough?
    - Eat first, then take pills on a full stomach
    - Hydration VERY important
- Cyclophosphamide (Cytoxan)
  - Food may help reduce GI side-effects

XELODA(R) Package Insert © 2011.

OC with Food

- Regorafenib (Stivarga)
  - Studied in fasted state, with low-fat meal (319 cal, 8.2g fat) and high-fat meal (945 cal, 54.6g fat)
  - Optimal absorption & safety profile found to be with low-fat meal
  - PI gives recommendation for “low-fat” meal
    - 2 slices of white toast with 1 tbsp low-fat margarine and 1 tbsp jelly, 8 oz skim milk
    - 1 cup cereal, 8 oz skim milk, 1 slice of toast with jelly, apple juice and 1 cup coffee or tea

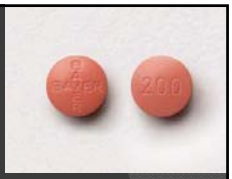
Stivarga ® Package Insert © 2013.

OC Empty Stomach

- Abiraterone (Zytiga)
  - Low-fat meal (7% fat, 300 cal) increased Cmax 7-fold & AUC 5-fold
  - High-fat meal (57% fat, 825 cal) increased Cmax 17-fold and AUC 10-fold
  - Since absorption highly variable based on composition of meals, med should be taken on a empty stomach
  - Controversy
    - Commentary in JCO by Mark Ratain
    - Suggested 1 tab daily with food may have been more “responsible” from the manufacturers

Ratain M. J Clin Oncol. 2011.
Zytiga ® Package Insert © 2012.

OC Empty Stomach



- Sorafenib (Nexavar)
  - High fat meal (50% fat, 900 cal) absorption reduced 29% vs. fasting
  - Moderate fat meal (30% fat, 700 cal) absorption similar to fasting
  - Manufacturer recommends taking on an empty stomach
  - Common side-effect: Abdominal pain
    - Anecdotal evidence: can take with a small low-fat snack to reduce GI symptoms

Nexavar ® Package Insert © 2013.

OC Who knows?

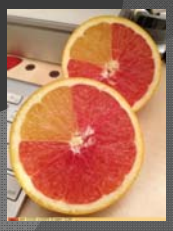
- Ibrutinib (Imbruvica)
  - PI specifically states AUC doubles if taken with food.
  - FDA approved with no recommendation to be taken with or without food
    - Why?
    - Wide therapeutic index?
  - Possible first step for mild side-effects, ensure taking on empty stomach

Question

- What is the primary issue in consuming grapefruit with certain drugs?
  - A) It tastes horrible unless covered in sugar
  - B) The acid content breaks down active drug
  - C) Depends on the type of grapefruit
  - D) It alters the metabolism of drugs in the body
  - E) It looks nothing like a grape

The Grapefruit Issue

- The Grapefruit
  - Developed in the 1700s as a cross between an orange and a shaddock (Pomelo)
- Active component
  - Furanocoumarins (bergamottin & its metabolites) confirmed to be the primary cause of the drug interaction



Kiani J & Imam SZ. Nutrition Journal. 2007
Van Erp NP, et al. Cancer Chemother Pharmacol. 2011

The Grapefruit Issue

- Pharmacologic Effect
  - Has significant CYP3A4 inhibiting effects
    - Mostly intestinal, but also in the liver
    - Can reduce enzyme activity by up to 50% and last more than 24 hours after consumption
  - May also affect other drug metabolism enzymes
- Result
  - Elevation in exposure to anti-cancer drugs leading to increased toxicity
  - Nilotinib & etoposide have best data
  - Most other drugs are extrapolated

Kiani J & Imam SZ. Nutrition Journal. 2007
Van Erp NP, et al. Cancer Chemother Pharmacol. 2011

The Grapefruit Issue

Drug-Grapefruit Interactions	
Afatinib (Gilotrif)	Gefitinib (Iressa)†
Axitinib (Inlyta)	Imatinib (Gleevec)
Bexarotene (Targetin)*	Ibrutinib (Imbruvica)
Cabozantinib (Cometriq)	Lapatinib (Tykerb)
Crizotinib (Xalkori)	Nilotinib (Tasigna)
Dabrafenib (Tafinlar)	Pazopanib (Votrient)
Dasatinib (Sprycel)	Ponatinib (Iclusig)
Erlotinib (Tarceva)*‡	Regorafenib (Stivarga)
Etoposide (VePesid)*	Ruxolitinib (Jakafi)
Everolimus (Afinitor)	Sunitinib (Sutent)*

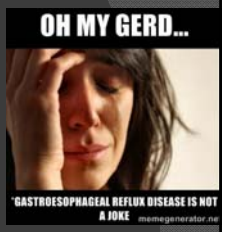
*Interaction listed as "moderate"
† Drug not available on US Market (limited distribution)
‡ Interaction decreases circulating levels of drug

Segal E, Flood M, Mancini R et al. Publication pending.

The Grapefruit Issue

- Recommendations
  - Make sure patients understand the issue
  - Avoid regular intake of grapefruit juice or grapefruit
  - Do not "freak out" about a one-time consumption
  - May also include Seville Oranges

Acid-Suppression Therapy

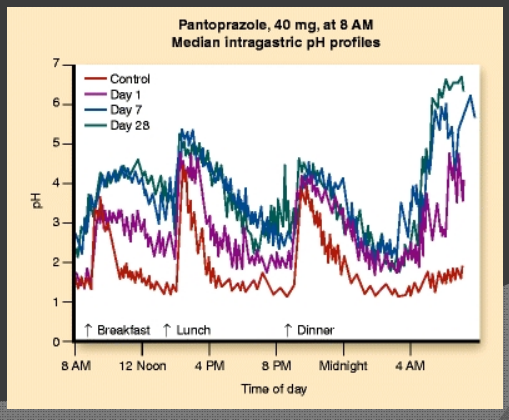


- New generation tyrosine kinase inhibitors (TKIs) require acidic environment (pH<5) for maximal absorption
- Many also require empty stomach due to changes in pH with food intake
- Drugs to consider
  - Proton-Pump Inhibitors (PPIs)
  - Histamine Receptor Antagonists (H2RAs)
  - Antacids

Robinson M. Aliment Pharmacol Ther. 2004

Acid-Suppression Therapy

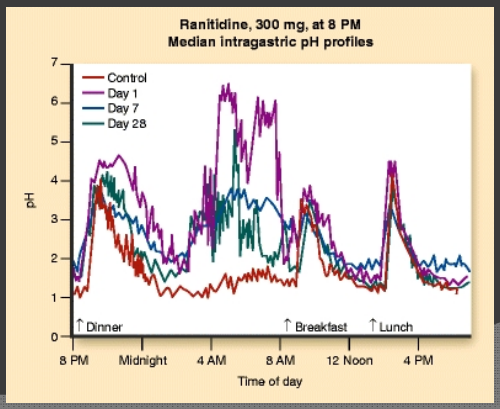
- Proton Pump Therapy
  - Duration of Action is >24 hours with repeated dosing



Sachs G. Curr Gastroenterol Rep. 2010

Acid-Suppression Therapy

- Histamine Receptor Antagonists
  - Duration of Action is ~12 hours



Sachs G. Curr Gastroenterol Rep. 2010

Acid-Suppression Therapy

- Acid Suppression reduces absorption and possibly efficacy

Drugs with Acid Suppression Issues
Bosutinib (Bosulif)*
Crizotinib (Xalkori)†
Dabrafenib (Tafinlar)†
Dasatinib (Sprycel)
Erlotinib (Tarceva)*
Gefinitib (Iressa)
Nilotinib (Tasigna)*
Ponatinib (Iclusig)†
Vismodegib (Erivedge)†

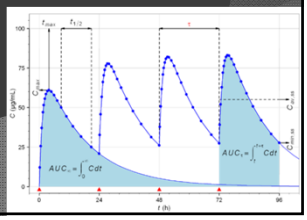
*Ok to use H2RA if appropriately spaced per PI.

† Solubility is pH dependant, interaction theoretical, no formal studies conducted

Segal E, Flood M, Mancini R et al. Publication pending.

Pharmacokinetic Studies

- Bosutinib (Bosulif)
  - Cmax ↓ 46%, AUC ↓ 26% after PPI
- Erlotinib (Tarceva)
  - Cmax ↓ 61%, AUC ↓ 46% after PPI
  - AUC ↓ 33% after H2RA
  - AUC ↓ 15% with appropriate spacing of H2RA
- Nilotinib (Tasigna)
  - AUC ↓ 34% after PPI
  - Efficacy doesn't appear to be affected



TARCEVA ®. Astellas Pharma. 2012. *BOSULIF ®. Pfizer Inc. 2012.*
TASIGNA ®.Novartis Pharmaceuticals. 2013. *Yin. Cancer Chemother Pharmacol. 2012*

Acid-Suppression Therapy

- Recommendations
  - Avoid PPIs for ALL listed drugs
    - Weigh pros & cons (ex. Recent GI Bleed)
    - Not a "contraindication"
  - H2RAs may be utilized in some situations
    - Avoid as much as possible
    - Hard to time with twice daily drugs
    - TKI should be taken 10 hours after or 2 hours before a dose of H2RA
  - Antacids are optimal choice
    - Separated by 2 hours from any agent used

Segal E, Flood M, Mancini R et al. Publication pending.

Lactose Intolerance

- Consider lactose intolerance in patients with treatment-associated diarrhea
  - Section 11 “Description” of package insert lists inactive ingredients
- Some agents are associated with diarrhea, but may also have primary lactose intolerance making it worse
- Lactase enzyme supplementation 30-60 min prior to dosing can help

Segal E, Flood M, Mancini R et al. Publication pending.

Lactose Intolerance

Agents with Lactose
Afatinib (Gilotrif)
Dasatinib (Sprycel)
Deferasirox (Exjade)*
Nilotinib (Tasigna)
Ponatinib (Iclusig)

*Supportive care medication, improper dissolution of drug can also increase diarrhea

Segal E, Flood M, Mancini R et al. Publication pending.
EXJADE ®. Novartis. 2013.

Deferasirox (Exjade) Dissolution

- Comes in dispersible tablets that must be fully dissolved to reduce risk of diarrhea
  - Doses <1 g in 3.5oz water or juice
  - Doses >1 g in 7oz water or juice
- Website has “step by step” web example
- Manufacturer has mixer cups available

EXJADE ®. Novartis. 2013.

Antioxidants

- Patient’s often like to utilize to “prevent” cancer and reduce toxicity
  - High antioxidant foods may reduce risk, but link to the antioxidants themselves is weak
- Several studies of supplements have shown no direct link in lower cancer risk
  - Beta-carotene: two studies showed increased risk of lung cancer (instead of prevention)
    - High-dose beta-carotene supplements should be avoided, especially in smokers
- Do antioxidants interfere with chemo?
- ACS Recommendation: Best to get through food and not utilize supplements

American Cancer Society. © 2012

Vitamins & Minerals

- Some agents bind minerals or polyvalent cations reducing absorption

Oral Agent	Interaction	Recommendation
Eltrombopag (Promacta)	Al*, Ca, Mg, Se, Zn, Fe	Avoid dairy products or Ca-rich foods, antacids & supplements for 4 hours surrounding doses
Erlotinib (Tarceva)	Polyvalent Cations	Take on empty stomach, separate supplements or antacids by 2 hours
Estramustine (Emcyt)	Calcium	Avoid dairy products & Ca supplements around dosing
Mercaptopurine (6-MP)	Calcium	Avoid dairy products & Ca supplements around dosing

*Drugs like Maalox, Mylanta and sucralfate have aluminum salts in them

Ricardi R. Pediatr Hematol Oncol. 1986
Segal E, Flood M, Mancini R et al. Publication pending.

Vitamins & Minerals

- Some vitamins interfere with actions of agents decreasing efficacy or increasing toxicity
- Bexarotene (Targretin) & Tretinoin (Vesanoid)
  - Activates retinoic acid receptors
  - Heavy Vitamin A supplementation can lead to Vitamin A toxicity
    - Nausea, fatigue, skin toxicity and cerebral edema
  - Limit Vitamin A intake to <15,000 IU/day.
- Capecitabine (Xeloda)
  - Oral more potent prodrug of 5-Fluorouracil (5-FU)
    - IV 5-FU often utilizes leucovorin (folinic acid) to agonize activity and increase activity
  - Folic acid supplementation increases toxicity
  - Limit folic acid to 100% RDA or less

XELODA®, Package Insert © 2011.
Targretin®, Ligand Pharmaceuticals 1999.

Question

- How much alcohol can a patient consume safely while on chemotherapy?
  - A) NONE, NEVER EVER!
  - B) A glass of wine or beer a day is fine
  - C) Depends on the drug treatment
  - D) Depends on the oncologist
  - E) Depends on if they are listening to this presentation

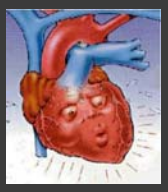
Alcohol

- In general alcohol intake should be limited during cancer treatment
  - ACS: 2 drinks per day men, 1 drink women
- Alcohol interacts more harshly with some agents and should be avoided

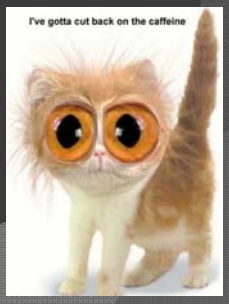
Oral Agent	Alcohol Interaction
Methotrexate (Trexall)	Increased hepatotoxicity
Nilutamide (Nilandron)	Ethanol intolerance (flushing, malaise, hypotension)
Procarbazine (Matulane)	Disulfiram-like reaction (flushing, headache, drowsiness)

Almeyda J. Br J Dermatol. 1971
Decensi A. Eur J Cancer. 1991.
Matulane ®. Roche Laboratories Inc. 1993.

Other Foods



- Procarbazine (Matulane)
  - Has MAO-I effects
  - Avoid tyramine rich foods
    - Wine, Yogurts, banana, aged cheeses, etc
  - Can cause hypertensive crisis
- Vemurafenib (Zelboraf)
  - Limit caffeine intake
  - Can augment caffeine effects
    - Agitation, rapid heart rate, insomnia



Brown CS & Bryant SG. Drug Intell Clin Pharm. 1988
Zelboraf™ Hoffmann-La Roche Inc.,2011.

Conclusions

- Oral chemotherapy management requires a multidisciplinary team
- Food-drug interactions play a part that does not exist with IV chemotherapy
- Dietary/Nutrition counseling is crucial to optimal management of oral chemotherapy patients
- Oncology Dietitians can play a huge role in managing food drug interactions

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Original Contribution

Oral Chemotherapy Food and Drug Interactions: A Comprehensive Review of the Literature

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Abstract

Introduction: Oral chemotherapy is rapidly becoming a popular dosage form for cancer treatment. These medications have a narrow therapeutic index, and their metabolism can be easily affected by food and/or drug interactions. These interactions can significantly reduce the effectiveness of oral chemotherapy, which could possibly result in harm to patients.

Methods: A systematic evaluation of 58 oral chemotherapeutics was conducted. Drug and food interactions were analyzed using US Food and Drug Administration–approved product labeling, primary literature, and tertiary databases.

Results: Our evaluation identified information about drug and food interactions. We present the recommended dose adjustments in our article.

Conclusion: Oral chemotherapy is associated with a significant number of medication and food interactions. It is essential that health care providers evaluate patients' diet and concurrent medications to provide accurate patient education, therapeutic monitoring, and, if necessary, alternative recommendations whenever oral chemotherapy is prescribed.

Introduction

Oral chemotherapy treatments have been available since 1953 and include familiar agents such as chlorambucil, mercaptopurine, and methotrexate—agents that are still used heavily in cancer treatment today. Since 1997, there has been a rapid influx of new oral chemotherapeutics, a broad pharmacologic class that includes oral cytotoxic agents and small-molecule inhibitors that target surface proteins, tumor biologic pathways, and receptors.[1] At the time of this review, > 30 new oral chemotherapeutics had been approved since 1998, when the US Food and Drug Administration first approved capecitabine. Furthermore, the National Comprehensive Cancer Network task force estimates that at least one fourth of the > 400 chemotherapeutics in the research pipeline are oral.[1]

Oral chemotherapy can offer patients convenience and an improved quality of life. For example, oral chemotherapy treatment offers less interference with work and social activities, avoidance of painful injections and prolonged infusion times, and more ownership over therapy with self-administration. According to a recent survey, 80% of patients said they would prefer oral chemotherapy treatment, assuming these agents were equally efficacious to parenteral therapy.[2] Additionally, in some cases, oral chemotherapy (ie, topoisomerase I inhibitors and fluoropyrimidines[2]) is capable of providing a more prolonged drug exposure than parenteral therapy and may, therefore, be a more effective delivery option for chemotherapeutics.

However, even with these benefits, oral chemotherapy treatment presents challenges to health care providers and patients. For example, to maximize the effectiveness of oral chemotherapy regimens, health care practitioners need to monitor patient adherence, review all potential food interactions, and evaluate the pharmacokinetic properties of these cytotoxic agents with other concomitant medications.

Health care providers also need to be vigilant about common misconceptions and safety issues regarding this class of medications. One common misconception is that oral chemotherapy is safer and less toxic than intravenous chemotherapy. However, drug and food interactions are ubiquitous among the broad class of oral chemotherapeutics, which can contribute to enhanced treatment-related toxicities. In fact, drug interactions are estimated to account for approximately 4% of deaths among patients with cancer.[3] Another major concern is that the types and levels of safeguards built into computerized physician order entry systems are not standardized and vary among each system implemented across health care facilities. Studies have suggested that computerized physician order entry systems may avoid potentially life-threatening events; however, errors still persist because of bypassing of alerts as well as weight, height, and unit discrepancies.[4]

Methods

A systematic review of 58 oral chemotherapeutic package inserts and primary literature from 1971 to 2013 was performed to verify drug-drug and drug-food interactions for all oral chemotherapeutics approved by the US Food and Drug Administration. Additionally, tertiary databases such as Micromedex 2.0 (www.micromedexsolutions.com) and Lexi-Comp

Table 1. Oral Chemotherapeutic Classification

Inhibitor/ Inducer	Change in AUC	Clearance of Medication (%)
Strong	>Five-fold	>80
Moderate	Two- to five-fold	50 to 80
Weak	1.25 to two-fold	20 to 50

NOTE. Data adapted.[5,6]
Abbreviation: AUC, area under the curve.

(www.lexi.com) were also referenced. Each medication was individually evaluated.

Drug-Drug Interactions

Drug-drug interactions were evaluated using sections 7.1 and 12.3 of the most recent package insert available of each medication at the time of this study. Each medication was assessed for specific drug-drug interactions and pharmacokinetic properties. Furthermore, each oral chemotherapeutic was evaluated for its specific enzyme substrates as well as cytochrome (CYP) induction and inhibition potential.

The following definitions were assumed for purposes of this review: A substrate was defined as a biologic enzyme for which a medication has an affinity. An oral chemotherapeutic was defined as an inducer or inhibitor if the medication raised or lowered the plasma concentration of another medication that was metabolized by that enzyme. Accordingly, oral chemotherapeutics were classified according to their levels of interaction and the clearance of medications (Table 1). An oral chemotherapeutic was considered to be a strong inhibitor or inducer if its interactions caused change in the area under the curve (AUC) of a substrate by at least five-fold or changed the clearance of a medication > 80%. An oral chemotherapeutic was classified as a moderate inhibitor or inducer if its interactions changed the AUC of a substrate by at least two- to five-fold or changed the clearance of a medication by 50% to 80%. An oral chemotherapeutic was deemed to be a weak inhibitor or inducer if its interaction changed the AUC by 1.25- to two-fold or changed the clearance of a medication by 20% to 50%.[5,6]

CYP450 inducers, inhibitors, and substrates were separated by the severity of their interactions (ie, mild, moderate, or major). P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and uridine diphosphate glucuronyltransferase (UGT), all of which were listed as either major or minor substrates, were included in this study if an interaction was specified in the literature. Recommended dose changes based on CYP interactions were also included if they were listed in the package insert. Each oral chemotherapeutic was categorized by its capacity to inhibit or induce CYP450, UGT, and P-gp. The specific enzymes evaluated for this review are listed in Table 2.

Oral chemotherapeutics were also analyzed for interactions with acid suppressor medications such as proton-pump inhibitors (PPIs), histamine 2-receptor antagonists (H2RAs), and antacids. Each oral chemotherapeutic was also evaluated for its effects on coumarin-containing products and its potential to prolong the QTc interval. These interactions were categorized as yes, no, or not studied. If a definite negative or positive interaction was provided by the package insert, the notation "no" or "yes" was used. However, if there was a lack of information pertaining to a specific drug or metabolism interaction, the notation "not studied" was used.

Table 2. Evaluated Enzymes

	Inhibited/Induced		
Enzyme	CYP450	UGT Pathway	ABC/BCRP
1A1		X	
1A2	X		
1A3		X	
1A4		X	
1A6		X	
1A9		X	
2A6	X		
2B6	X		
2C8	X		
2C9	X		
2C19	X		
2D6	X		
2E1	X		
3A4	X		
3A5	X		
3A7	X		
ABCG2			X
BCRP			X
OABP			X

Abbreviations: ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; CYP450, cytochrome P450; UGT, uridine diphosphate glucuronyltransferase.

Drug-Food Interactions

Section 2.1 and the absorption subheading of section 12.3 of the package insert for each medication were reviewed to evaluate drug-food interactions. Sections 7.1 and 11 were evaluated to determine whether the medication contained lactose or interacted with grapefruit juice. The specific recommendations for timing and the effects of food on maximum concentration (C_{max}) and AUC were also analyzed. All items discovered in the referred sections were documented, and a chart was created outlining each of these parameters. Data were cross-referenced to the Micromedex 2.0 food interaction checker and confirmed through the Lexicomp online database. Any additional information based on published postmarketing studies provided by these references or PubMed that was not addressed in the package inserts was included under Food-Related Considerations in Table 3.

Results

Drug-Drug Interactions

Our survey covered 58 oral chemotherapeutics, including 49 oral chemotherapies, seven hormonal agents, and two support-

Table 3. Drug-Food Interactions

Medication	Food Interactions: Take With Food	Food Interactions: Take on Empty Stomach*	Food Interactions: Grapefruit Interaction	Food-Related Considerations
Abiraterone		X		High-fat meals can increase total systemic exposure 10-fold[7]
Afatinib		X		High-fat meals can decrease C_{max} and AUC values by 50% and 39%, respectively
Altretamine	X			
Anastrozole				
Axitinib			X	
Bexarotene	X		Moderate	
Bicalutamide				
Bosutinib	X			
Busulfan				
Cabozantinib		X	X	High-fat meal increased C_{max} and AUC values by 41% and 57%, respectively[8]
Capecitabine	X			Taking with food, preferably after meal, creates more even absorption and decreases adverse effects; avoid excessive folate supplementation (< 100% RDA okay), which can increase toxicity
Chlorambucil		X		
Crizotinib			X	
Cyclophosphamide	X			Take in morning and drink plenty of fluids throughout day to flush metabolites and protect bladder; food may help reduce GI adverse effects
Dabrafenib		X	X	When coadministered with PPI, H2RA, or antacid, systemic exposure may be decreased; however, it has not been studied whether this affects efficacy
Dasatinib			X	Tablets contain lactose; consider lactose intolerance; requires acidic environment for absorption; caution for those using acid suppression therapy
Deferasirox		X		Tablets contain lactose; consider lactose intolerance; tablets must be dissolved completed; incomplete dissolution can lead to diarrhea
Eltrombopag		X		Avoid calcium or dairy products for 4 hours surrounding dosing time, because these can reduce absorption
Enzalutamide				
Erlotinib		X	Moderate	Active smokers can increase metabolism of drug, thereby reducing effectiveness; requires acidic environment for absorption; caution for those using acid suppression therapy
Estramustine		X		Capsules must remain refrigerated; avoid calcium or dairy products, because these can reduce absorption[9]
Etoposide			Moderate	Grapefruit juice decreases VP-16 levels; medication must remain refrigerated[10]
Exemestane	X			
Everolimus			X	Can cause metabolic changes, including hypercholesterolemia and hyperglycemia; monitor metabolic panels
Flutamide				
Gefitinib			X	For patient with difficulty swallowing, tablets may be dissolved in half glass of noncarbonated drinking water only; stir tablet until dispersed (approximately 10 minutes), and drink liquid immediately; rinse glass with another 4 ounces of water and drink; solution can be administered via NG tube; requires acidic environment for absorption; caution for those using acid suppression therapy
Hydroxyurea				Capsules may be opened and dissolved in water; use proper chemotherapy handling precautions[11]
Ibrutinib			X	Per package insert: avoid Seville oranges due to their potential to moderately inhibit CYP3A4. Capsules should be taken orally with a glass of water. Do not open, break, or chew the capsules
Imatinib	X		X	Tablets may be dispersed in water or apple juice; stir until dissolved, and use immediately
Lapatinib		X	X	Food increases total exposure to medication, increasing adverse effects
Lenalidomide				
Letrozole				

Continued on next page

Table 3. (Continued)

Medication	Food Interactions: Take With Food	Food Interactions: Take on Empty Stomach*	Food Interactions: Grapefruit Interaction	Food-Related Considerations
Lomustine		X		Can be taken with or without food; however, taking on empty stomach at bedtime reduces nausea
Melphalan		X		Medication must remain refrigerated; although not stated in PI, PK studies show decreased absorption if taken with food[12]
Mercaptopurine		X		Although not stated in PI, medication may be best absorbed on empty stomach; avoid dairy or calcium products within 2 hours of dose; tablets may be crushed; use proper handling precautions[13]
Methotrexate				Take in morning, and drink plenty of fluids throughout day to reduce risk of kidney damage; concomitant use of alcohol may increase risk of hepatotoxicity[14-16]
Mitotane				
Nilotinib		X	X	Tablets contain lactose; consider lactose intolerance; requires acidic environment for absorption; caution for those using acid suppression therapy; if patient cannot swallow, capsules may be opened and sprinkled on 1 tbsp of applesauce[17]
Nilutamide				Concomitant use of alcohol may result in ethanol intolerance (facial flushing, malaise, and hypotension)[18]
Pazopanib		X	X	Food increases total exposure to medication, increasing adverse effects
Pomalidomide		X		Per package insert, take 2 hours before or 2 hours after meals
Ponatinib			X	Tablets contain lactose; consider lactose intolerance; requires acidic environment for absorption; caution for those using acid suppression therapy
Procarbazine				Avoid tyramine-rich foods (eg, wine, yogurt, bananas, aged cheeses), because this may precipitate hypertensive crisis[19]; concomitant use of alcohol may cause disulfiram-like reaction and sedation
Regorafenib	X		X	Take with low-fat breakfast
Ruxolitinib			X	
Sorafenib		X		Can take with piece of bread or cracker (low-fat snack) if experiencing abdominal discomfort with dosing
Sunitinib			Moderate	May cause oral irritation and taste disturbances
Tamoxifen				
Temozolomide		X		Taking with food can reduce rate and extent of medication absorbed by body, increasing adverse effects; taking at bedtime can reduce nausea experience
Thalidomide		X		
Thioguanine				
Topotecan				
Trametinib		X	Not studied	
Tretinoin				
Vandetanib				If tablets cannot be swallowed whole, dispersion can be made with 2 ounces of noncarbonated water only; stir for approximately 10 minutes and administer immediately; rinse glass with additional 4 ounces of water and drink; tablets may not fully dissolve
Vemurafenib				This medication can augment effects of caffeine
Vismodegib				Requires acidic environment for absorption; caution for those using acid suppression therapy
Vorinostat	X			

Abbreviations: AUC, area under the curve; C_{max}, maximum concentration; H2RA, histamine 2-receptor antagonist; NG, nasogastric; PI, package insert; PK, pharmacokinetic; PPI, proton-pump inhibitor; RDA, recommended dietary allowance.
* Empty stomach indicates medication should be taken 1 hour before or 2 hours after last meal.

ive care medications. We noted the following primary drug interactions:

The CYP450 enzyme class was the predominant substrate for oral chemotherapeutics, involving 41 medications. The P-gp, BCRP, and UGT enzyme classes were substrates for 18, four, and five medications, respectively. A majority of the medications analyzed involved multiple substrates in their metabolism, the most prevalent combination of which was CYP450 enzymes plus P-gp.

Our study of drug interactions revealed that the addition of an oral chemotherapeutic to an anticoagulant may have unpredictable effects on the international normalization ratio (INR).

Approximately 16 of the oral chemotherapeutics affected the absorption of coumarin-derived anticoagulants, and prolongation of the QTc interval was remarkable in 14 agents. Only one oral chemotherapy—vandetanib—had a black-box warning for QTc prolongation and sudden death. Additionally, any other drug-drug interactions that had specific dose-modification recommendations available in the package insert or through tertiary databases were listed for 16 oral chemotherapeutics (Appendix Table A1, online only). Finally, we also noted that acid suppression affected absorption rates for nine oral chemotherapeutic agents.

Drug-Food Interactions

The following drug-food interactions were noted for the 58 oral chemotherapeutics in our study. For nine drugs, ingestion with food was recommended, whereas 20 required that they be taken on an empty stomach. The fat content of a patient's meal was noted as important in the total absorption of four of those medications advised to be taken on an empty stomach. Three drugs were noted to have interactions with calcium-containing foods or supplements, and nine drugs had pH-dependent absorption. Four of the oral chemotherapeutics noted significant quantities of lactose in the pills as inactive ingredients (Table 3). In addition, clinically significant and moderate interactions with grapefruit were noted in 15 and four drugs, respectively.

Discussion

Health care professionals need to take into account a variety of factors when considering the use of oral chemotherapeutic agents, especially for patients with comorbidities. Oral chemotherapeutics have a fairly narrow therapeutic index, and potential drug interactions between oral chemotherapeutics, concomitant medications, and gastric acid suppression can cause significant changes in the bioavailability of oral chemotherapeutics.

A majority of oral chemotherapeutic agents show little or no interaction with acid suppression therapy, but there are some notable exceptions. Evidence for some of these interactions is strong, whereas others remain mostly theoretic. The package inserts for dasatinib, erlotinib, and ponatinib carry warnings to avoid PPIs because the drugs require an acidic environment to be fully absorbed. Acid suppression should be avoided when dastinib is prescribed; however, the use of antacids 2 hours after administration is permitted.[20-22] The absorption of erlotinib has been shown to be definitively decreased when coadministered with both PPIs and H2RAs. Concomitant administration of erlotinib and PPIs should be avoided. If acid suppression is necessary, erlotinib and H2RA therapy may be coadministered if deemed necessary, provided erlotinib is taken 10 hours after or 2 hours before a dose of any H2RA. Lastly, the extent to which ponatinib is affected by acid suppression is not well defined, and the package insert strongly recommends avoidance of all acid suppression therapy when using the medication.[23]

Manufacturers of several other oral chemotherapeutics recommend that avoidance of PPIs be considered. Bosutinib and nilotinib have demonstrated decreased absorption with concomitant PPI therapy. The recommendation for bosutinib is to avoid PPIs and use H2RAs instead, if possible.[24] The AUC of nilotinib is significantly decreased with concominant administration of PPIs. However, several studies suggest that clinical outcomes are unaffected by this combination.[25-27] PPIs interact with methotrexate, resulting in a delayed elimination, and therefore have the potential to cause methotrexate toxicity.[28] It has been observed that methotrexate concentrations are increased (in a dose-dependent manner) with concomitant PPI use; therefore, toxicities need to be more carefully monitored when considering this interaction.[29,29a] However, unless toxicities are patient reported or reflected in serum methotrexate levels, their interactions are unlikely to result in therapeutic modifications.[28]

Health care providers also need to consider that acid suppression with PPIs is a drawn-out process. For example, pH holding times (ie, stomach pH maintained $>$ 4 hours) of all PPIs will likely persist beyond the 24-hour dosing schedule for most patients after 5 days of therapy.[29] Timing doses to avoid a drug interaction would therefore be a futile exercise. The duration, indication, and frequency of PPIs vary; abrupt cessation of the medications may not be a viable option, especially in cases where a patient may have Barrett's esophagus or a history of GI bleeding.

There is a wide spectrum of recommendations on ways to manage drug-drug interactions across the broad class of oral chemotherapeutics. Although some drug interactions can be easily managed by an increase in monitoring using laboratory tests and patient tolerance, greater monitoring cannot mitigate the impact of others. The interaction between coumarin-derived anticoagulants and oral chemotherapeutics can potentially elevate INR; thus, greater vigilance when treating patients is required. However, certain oral chemotherapies with coumarin-derived anticoagulants cannot be managed with increased monitoring. For example, the concurrent use of warfarin and tamoxifen is contraindicated because tamoxifen has the potential to inhibit CYP2C9, resulting in a significant increase in anticoagulant effect and therefore a substantially increased risk of bleeding.[30,31] Enzalutamide is the only oral chemotherapeutic that may decrease the serum concentration of warfarin; however, this drug-drug interaction can be managed by increased monitoring of patients' INR.

Food interactions can be difficult to manage for patients receiving oral chemotherapy because of the lifestyle changes they might require, even if changes apply only to daily regimens, one meal a day, or time of day medication is taken. Changes in lifestyle can adversely affect the likelihood of adherence. Although defining an empty stomach as ingesting medications 1 hour before or 2 hours after meals might simplify the requirement, it might not necessarily make it any easier for a patient to adjust his or her daily routine. For example, although the manufacturer of regorafenib recommends that patients take the medication with a low-fat breakfast, it is up to the health care provider to carefully instruct the patient on the meaning and implications of this requirement. In fact, although the patient counseling information accompanying this drug elabo-

rates on this requirement, the definition is fairly specific and cannot account for restrictions or variability in a patient's diet. It is for these reasons that consultation and collaboration with clinical oncology dietitians can be beneficial.

Most food interactions result from the relative fat content in food being consumed. In 2011, a commentary in *Journal of Clinical Oncology* by Dr Mark Ratain brought to light the issue of food interactions and their impact on oral chemotherapy development, thereby reshaping prescription and dietary recommendations for patients who take these medications.[32] The variability in drug absorption based on relative fat content cannot account for interpatient variability. As a result, manufacturers have to make choices on what is safest for the general population. In some cases, like with abiraterone or regorafenib, the package insert fully details the interaction, specifically stating, for example, "abiraterone C_{max} and AUC were approximately seven- and five-fold higher, respectively, when abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10-fold higher, respectively, when abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal."[7] In other situations, some package inserts, like cabozantinib, outline the effects of a high-fat meal as increasing C_{max} and AUC values by 41% and 57%, respectively, without defining a threshold for high-fat content.[8] On the basis of variations in absorption, most manufacturers have simply recommended that medications be taken on an empty stomach, and commentaries on this development can often be too narrowly focused.

There are a few limitations to the methodology followed in this article. We relied on the most recent versions of the package inserts to identify and highlight specific interactions. Unfortunately, some of the oral chemotherapeutics that have been on the market for a substantial time do not have current studies pertaining to specific drug-drug and drug-food interactions. Second, certain drug-drug interactions were not included in our analysis because of a pharmacodynamic interaction rather than a pharmacokinetic interaction. Therefore, it is important for health care professionals to evaluate pharmacodynamic interactions when prescribing oral chemotherapy. Lastly, the literature for oral chemotherapy changes swiftly; the tables provided in this article reflect the most current recommendations at the time data were collected. Therefore, it is imperative that health care providers actively review the most current data for drug-drug and drug-food interactions before making any formal recommendations.

In conclusion, the patient population receiving oral chemotherapeutics is increasing rapidly, causing stark changes in the management and treatment of malignancies. Increased use of oral chemotherapy can be attributed to improvements in screening, technology, and overall number of available products. It is imperative that health care providers monitor patients for potential food-drug and drug-drug interactions to avoid a loss in efficacy or increased risk of toxicity from oral chemotherapy. Oncology pharmacists who specialize in oral chemotherapy can play an essential role in maintaining patient safety. The pharmacist can provide medication counseling and dosing recommendations and can render vital toxicity management services when drug-drug and/or drug-food interactions are relevant.[33]

Authors' Disclosures of Potential Conflicts of Interest

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Appendix

Table A1. Drug-Drug Interactions

Oral Oncologic	Substrate	Competitive Inhibitor	Competitive Inducer	Effect of Acid Suppression on Absorption	Warfarin Effects	QTc Prolongation	Drug-Related Considerations
Abiraterone (Zytiga, Janssen Biotech, Horsham, PA)[7]	3A4*	2D6+++, 1A2+++, 2C19++, 2C9++, 3A4++, 2C8+++		None	No	No	
Afatinib (Gilotrif, Boehringer Ingelheim, Ridgefield, CT)[9]	BCRP, P-gp	BCRP, P-gp		Not studied	No	No	P-gp inhibitors/inducers: reduce/increase afatinib by 10 mg per day if concomitant P-gp inhibitors/inducers are to be used Contraception: women should use contraception during treatment and ≥ 2 weeks after last dose of afatinib
Altretamine (Hexalen package insert: Bloomington, IN, MGI Pharma, 2001)				None	No	No	No known transporter effects MAOIs: use caution with concurrent administration with MAOIs, because severe orthostatic hypotension may result
Anastrozole (Arimidex package insert: Wilmington, DE, AstraZeneca, 2013)	1A2+	2C8+, 2C9+, 3A4+		None	No	Not studied	Estrogen: do not use estrogen-containing products with anastrozole
Axitinib (Inlyta package insert: New York, NY, Pfizer, 2013)	3A4*, 3A5*, 1A2−, 2C19−, UGT1A1			None	No	No	CYP3A4/5 inhibitors (strong): avoid combination; however, if combination warranted, decrease dose of axitinib by 50%; if strong CYP3A4/5 inhibitor discontinued, increase axitinib dose to original dose used before reduction
Bexarotene (Targretin package insert: San Diego, CA, Ligand Pharmaceuticals, 2000)	3A4−		3A4+	Not studied	Not studied	Not studied	Gemfibrozil: avoid combination Vitamin A: limit intake to ≤ 15,000 IU/day Hormone-containing contraceptives: bexarotene can increase metabolism of contraceptives; nonhormonal contraceptives should be used
Bicalutamide (Casodex package insert: Memphis, TN, Northstar Rx, 2011)		3A4++		None	Yes	No	Coumarin-derived products: bicalutamide can displace coumarin from binding sites; monitor PT/INR
Bosutinib (Bosulif package insert: New York, NY, Pfizer, 2013)	3A4*, Pg-p	P-gp		Yes	No	Yes	H2 antagonists and antacids: H2 antagonists decrease concentration of bostunib; H2RAs or antacids should be administered 2 hours before or after bosutinib therapy PPIs: decrease concentration of bosutinib; avoid combination; switch patient to antacids or H2RAs QTc: bosutinib may prolong QT interval
Busulfan (Myleran package insert: Research Triangle Park, NC, GlaxoSmithKline, 2005)	3A4*			Not studied	Not studied	Not studied	
Cabozantinib (Cometriq, Exelixis, San Francisco, CA)[8]	2C9−, 3A4*	P-gp		Not studied	Not studied	Possible	CYP3A4 inhibitors (strong): avoid combination; if combination cannot be avoided, reduce cabozantinib dose by 40 mg; once 3A4 inhibitor discontinued, resume original dose after washout period of 2 to 3 days QTc: cabozantinib may increase QT interval, but relationship cannot be definitively established

Continued on next page

Table A1. (Continued)

Oral Oncologic	Substrate	Competitive Inhibitor	Competitive Inducer	Effect of Acid Suppression on Absorption	Warfarin Effects	QTc Prolongation	Drug-Related Considerations
Capecitabine (Xeloda package insert: South San Francisco, CA, Genentech, 2011)		2C9+++		No	Yes	Not studied	Phenytoin: monitor phenytoin levels in patients taking capecitabine; dose adjustments may be warranted Antacids: antacids containing aluminum cations may increase concentration of capecitabine Coumarin-derived anticoagulants: capecitabine increases anticoagulant effect of coumarin-derived anticoagulants; monitor PT/INR closely
Chlorambucil (Leukeran package insert: Research Triangle Park, NC, GlaxoSmithKline, 2011)				Not studied	Not studied	Not studied	No metabolism or transport effects known
Crizotinib (Xalkori, Pfizer, New York, NY)[24]	3A4*, P-gp	3A4++, P-gp, 2B6+++		Possible	Not studied	Yes	QTc: crizotinib enhances QTc prolongation Acid suppression: crizotinib solubility pH dependent; PPI, H2 blockers, and antacids may decrease bioavailability of crizotinib
Cyclophosphamide (Cytoxan intravenous injection, oral tablets product information: Deerfield, IL, Baxter Healthcare, 2013; Viby-Mogensen J: Dan Med Bull 30:129-150, 1983)	2A6−, 2B6*, 2C19−, 2C9−, 3A4−	3A4+	2B6++, 2C9++	Not studied	Not studied	Not studied	Succinylcholine: cyclophosphamide can inhibit cholinesterase, potentiating effects of succinylcholine; if patient treated with cyclophosphamide within 10 days of receiving anesthesia, anesthesiologist should be notified
Dabrafenib (Tafinlar package insert: Research Triangle Park, NC, GlaxoSmithKline, 2013)	3A4, 2C8, P-gp, BCRP		3A4++, 2B6, 2C8, 2C19, UDP	Possible	Yes	Not studied	Acid suppression: dabrafenib solubility pH dependent; PPI, H2 blockers, and antacids may decrease dabrafenib bioavailability Warfarin: dabrafenib may decrease concentration of warfarin; monitor PT/INR appropriately; Nonhormonal contraceptives: women should be started on nonhormonal contraceptives at initiation of dabrafenib and continue therapy until 4 weeks after discontinuation; dabrafenib may affect metabolism of hormonal contraceptives and decrease their effectiveness
Dasatinib (Sprycel, Bristol-Myers Squibb, Princeton, NJ)[27]	3A4*	3A4+		Yes	Possible	Yes	Anticoagulants: Dasatinib may enhance the antiplatelet activity. Use caution with agents that have antiplatelet properties (eg, coumarin, aspirin, NSAIDs) Acid suppression: H2 antagonists and PPIs decrease absorption of dasatinib; use antacids in place of H2 blockers and PPIs; antacids should be taken 2 hours before or after dasatinib; QTc: prolongs QT interval
Deferasirox (Exjade package insert: East Hanover, NJ, Novartis, 2013)	UGT1A1*	1A2++, 2C8++	3A4++	No	Yes	No	UGT inducers: UGT inducers decrease deferasirox bioavailability; avoid concomitant therapy; if deferasirox coadministration is warranted, consider increasing initial dose by 50%; monitor ferritin levels. Antacids containing aluminum hydroxide: avoid combination; may diminish effect of deferasirox

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Table A1. (Continued)

Oral Oncologic	Substrate	Competitive Inhibitor	Competitive Inducer	Effect of Acid Suppression on Absorption	Warfarin Effects	QTc Prolongation	Drug-Related Considerations
							Bile acid sequestrants: decrease serum concentration of deferasirox; avoid combination; if combination necessary, consider 50% increase in initial deferasirox dose; monitor ferritin levels Anticoagulants: anticoagulants enhance toxic effects of deferasirox (eg, GI ulceration, irritation, bleeding); deferasirox may increase INR; monitor appropriately
Eltrombopag (Promacta package insert: Research Triangle Park, NC, GlaxoSmithKline, 2012; Williams DD et al: Clin Ther 31:764-776, 2009)	1A2−, 2C8−, UGT1A1−, UGT1A3, BCRP*	2C8++, OATP1B+++, BCRP++, UGT1A1, UGT1A3, UGT1A4, UGT1A6		No	No	No	OATP1B1 and BCRP substrates: consider dose reduction in substrates of OARP1B1 and BCRP such as rosuvastatin; reduce dose of rosuvastatin by 50% during therapy initiation Antacids: do not take eltrombopag within 4 hours of products/medications containing polyvalent cations (eg, antacids, dairy products, mineral supplements)
Enzalutamide (Xtandi package insert: Northbrook, IL, Astellas Pharmaceuticals, 2012)	2C8*, 3A4*	P-gp	2C19++, 2C9++, 3A4+++	No	Yes	Possible	CYP2C8 inhibitors (strong): may increase serum concentration of enzalutamide; avoid combination; if combination must be used, reduce enzalutamide to 80 mg daily Coumarin: enzalutamide decreases concentration of warfarin; monitor INR QTc prolongation: small changes in QTc interval in placebo studies, but no formal conclusion can be drawn
Erlotinib (Tarceva package insert: Farmingdale, NY, OSI Pharmaceuticals, 2013)	3A4*, 1A2−			Yes	Yes	Not studied	Cigarette smoking: smoking reduces erlotinib exposure; if patient active smoker, increase dose of erlotinib; do not exceed 300 mg Antacids containing polyvalent cations: antacids decrease serum concentration of erlotinib; separate administration by several hours H2 antagonists: decrease serum concentration of erlotinib; avoid combination; if coadministration cannot be avoided, erlotinib should be dosed once daily, 10 hours after and ≥ 2 hours before H2 antagonist dosing PPIs: avoid combination; PPIs may decrease serum concentration of erlotinib Coumarin-derived anatagonists: erlotinib may increase INR; monitor appropriately
Estramustine (Emcyt package insert: New York, NY, Pfizer, 2007)				No	Not studied	Not studied	No known metabolism or transport effects Calcium and calcium-containing antacids: do not administer estramustine concomitantly with calcium-containing antacids or other calcium-containing products
Etoposide (VePesid package insert: Morgantown, WV, Mylan Pharmaceuticals, 2013)	P-gp−, 1A2−, 2E1−, 3A4*	3A4+, 2C9+		Not studied	Not studied	Not studied	No known metabolism or transport effects
Exemestane (Aromasin package insert: New York, NY, Pfizer, 2013)	3A4*		3A4++	Not studied	Not studied	Not studied	

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Table A1. (Continued)

Oral Oncologic	Substrate	Competitive Inhibitor	Competitive Inducer	Effect of Acid Suppression on Absorption	Warfarin Effects	QTc Prolongation	Drug-Related Considerations
Everolimus (Afinitor package insert: East Hanover, NJ, Novartis, 2012)	P-gp−, 3A4*			Not studied	Not studied	No	CYP3A4/P-gp inhibitors (moderate): use caution with everolimus and moderate 3A4/P-gp inhibitors; consider reducing everolimus dose to 2.5 mg daily; if moderate inhibitor discontinued, observe washout period of 2 to 3 days before increasing everolimus to original dose CYP3A4 inducers (strong): avoid use with strong CYP3A4 inducers; if therapy cannot be avoided, gradually (in 5-mg increments) increase dose from 10 to 20 mg/day
Flutamide (Eulexin product information: Kirkland, Quebec, Canada, Merck, 2012)	1A2*, 3A4*	1A2+		Not studied	Yes	Not studied	Warfarin: flutamide increases PT; monitor appropriately
Gefitinib (Iressa product information: Sodertalje, Sweden, AstraZeneca, 2009)	2D6*, 3A4*	BCRP, 2C19+, 2D6+		Yes	Yes	Not studied	CYP3A4 inducers (strong): may decrease serum concentration of gefitinib; consider increasing gefitinib dose to 500 mg daily PPIs and H2 antagonists: may decrease serum concentration of gefitinib Coumarin derivatives: gefitinib may enhance anticoagulant effect of coumarin-derived products; montior appropriately
Hydroxyurea (Hydrea package insert: Princeton, NJ, Bristol-Myers Squibb, 2011)				Not studied	Not studied	Not studied	No known metabolism or transport effects
Ibrutinib (Imbruivica package insert: Sunnyvale, CA, Pharmacyclics, 2013)	3A4*	P-gp+		Not studied	Not studied	Not studied	CYP3A4 inhibitors (strong): avoid combination; if strong CYP3A4 inhibitor is to be taken < 7 days, consider interrupting ibrutinib until strong CYP3A4 inhibitor discontinued; if strong CYP3A4 inhibitor is to be used chronically, reduce dose of ibrutinib to 140 mg daily; monitor for signs and symptoms of toxicity P-gp: may inhibit P-gp in GI tract; monitor P-gp substrate medications with narrow therapeutic index (eg, digoxin)
Imatinib (Gleevec package insert: East Hanover, NJ, Novartis, 2013)	Pg-P−, 3A4*, 1A2−, 2C9−, 2D6−, 2C19−	3A4++, 2C9+, 2D6++, BCRP++, P-gp		Not studied	Yes	Not studied	CYP3A4 inducers (strong): may decrease concentration of imatinib; if coadministration necessary, increase imatinib dose by ≥ 50%; imatinib doses ≤ 1,200 mg/day have been used in patients receiving strong 3A4 inducers Warfarin: may enhance anticoagulant effect of warfarin; monitor INR or consider changing to LMWH therapy
Lapatinib (Tykerb package insert: Research Triangle Park, NC, GlaxoSmithKline, 2013)	P-gp, 3A4*	P-gp, 3A4+, 2C8++, BCRP		Not studied	Yes	Yes	CYP3A4 inducers (strong): may decrease serum concentration of lapatinib; consider titrating lapatinib gradually from 1,250 to ≤ 4,500 mg/day (in HER2-positive metastatic breast cancer) or 1,500 mg/day to ≤ 5,500 mg/day (in hormone receptor/HER2-positive breast cancer) as tolerated CYP3A4 inhibitors (strong): may increase serum concentration of lapatinib; consider reducing dose to 500 mg/day during and within 1 week of completion of treatment with strong 3A4 inhibitors

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Table A1. (Continued)

Oral Oncologic	Substrate	Competitive Inhibitor	Competitive Inducer	Effect of Acid Suppression on Absorption	Warfarin Effects	QTc Prolongation	Drug-Related Considerations
							Dabigatran: may increase concentrations of dabigatran; consider reducing dabigatran dose (Pradaxa package insert: Ridgefield, CT, Boehringer Ingelheim, 2011) QTc: prolongs QT interval
Lenalidomide (Revlimid package insert: Summit, NJ, Celegene, 2013)	P-gp			Not studied	No	No	Digoxin: monitor digoxin plasma levels; lenalidomide may increase C_{max} and AUC of digoxin
Letrozole (Femara package insert: East Hanover, NJ, Novartis, 2011)	3A4−, 2A6−	2A6+++, 2C19+		No	No	Not studied	Tamoxifen: coadminstration of letrozole and tamoxifen can result in reduction of letrozole in plasma; administer letrozole immediately after tamoxifen
Lomustine (CeeNU package insert: Princeton, NJ, Bristol-Myers Squibb, 2012)	2D6−	3A4+, 2D6+		Not studied	Not studied	Not studied	
Melphalan (Alkeran package insert: Research Triangle Park, NC, GlaxoSmithKline, 2007)				Not studied	Not studied	Not studied	No known metabolism or transport effects
Mercaptopurine (Purinethol package insert: Greenville, NC, Gate Pharmaceuticals, 2011)				Not studied	Not studied	Not studied	No known metabolism or transport effects
Methotrexate (Trexall, Hospira, Lake Forest, IL; Erttmann R et al: J Cancer Res Clin Oncol 110:48-50, 1985; Tobias H et al: Arch Intern Med 132:391-396, 1973)[28]	P-gp, SLCO1B1			Not studied	Not studied	Not studied	Bile acid sequestrants: Bile acid sequstrants decrease absorption of methotrexate NSAIDs: increase serum concentration of methotrexate Loop diuretics: methotrexate diminishes therapeutic effects and increases serum concentrations of loop diuretics; loop diuretics may also increase serum concentration of methotrexate; monitor for toxicities and decreased therapeutic effects of loop diuretics; dose reductions for methotrexate and/or loop may be required (Lasix package insert: Bridgewater, NJ, sanofi-aventis, 2012)
Mitotane (Lysodren, Bristol-Myers Squibb, Princeton, NJ)[17]				Not studied	Yes	Not studied	No known metabolism or transport effects Warfarin: mitotane may increase metabolism of warfarin; monitor appropriately
Nilotinib (Tasigna, Novartis, East Hanover, NJ)[18]	CYP3A4*, P-gp	CYP3A4+, CYP2C9++, CYP2D6++, CYP2C8++, P-gp, UGT1A1	CYP 2B6++, CYP2C8++, CYP2C9++,	Yes	No	Yes	PPIs: avoid combination; separation of PPIs does not eradicate interaction; switch to H2 blocker or antacid H2 blockers and antacids: administer H2 blockers 2 hours before or 10 hours after; patients can take antacids, but separate administration by 2 hours before or after nilotinib administration QTc-interval: nilotinib may prolong QT interval
Nilutamide (Nilandron package insert: Kansas City, MO, Aventis Pharmaceuticals, 2005)	CYY2C19*	CYP2C19+		No	No	No	
Pomalidomide (Pomalyst package insert: Summit, NJ, Celegene, 2013)	CYP1A2*, CYP3A4*, CYP2D6−, CYP2C19−, P-gp			Not studied	Not studied	Not studied	Drug interaction studies for pomalidomide have not been conducted

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Table A1. (Continued)

Oral Oncologic	Substrate	Competitive Inhibitor	Competitive Inducer	Effect of Acid Suppression on Absorption	Warfarin Effects	QTc Prolongation	Drug-Related Considerations
Pazopanib (Votrient package insert: Research Triangle Park, NC, GlaxoSmithKline, 2013)	CYPAA4*, CYP1A2−, CYP2C8−, P-gp	CYP2C8+, CYP2D6+, CYP3A4+, SLCO1B1, UGT1A1		No	No	Yes	CYP3A4 inhibitors (strong): avoid combination; if combination must be used, reduce dose of pazopanib to 400 mg QTc: pazopanib prolongs QTc interval; monitor appropriately
Ponatinib (Iclusig, ARIAD Pharmaceuticals, Cambridge, MA)[23]	CYP2C8−, CYP2D6−, CYP3A4−, P-gp, BCRP		P-gp, BCRP	Possible	Not studied	No	CYP3A4 inhibitors (strong): reduce ponatinib dose to 30 mg daily if administered with strong CYP3A4 inhibitor Acid suppression: interaction between ponatinib and acid suppressers has not been formally studied; elevated pH may reduce bioavailability of pontatnib; combination should be avoided
Procarbazine (Matulane package insert: Gaithersburg, MD, Sigma-Tau Pharmaceuticals, 2008)		MAOI		No	Not studied	Not studied	MAOI: procarbazine has MAOI properties, which can enhance vasopresser and serotonergic effects; avoid sympathomimetic drugs and TCAs
Regorafenib (Stivarga package insert: Wayne, NJ, Bayer HealthCare, 2013)	CYP3A4*, UGT1A9	CYP2C8, CYP2C9, CYP2B6, CYP3A4, CYP2C19, UGT1A9, UGT1A1, BRCP, P-gp		Not studied	Yes	No	Warfarin: warfarin may enhance toxicities of regorafenib and increase risk of bleeding; monitor INR
Ruxolitinib (Jakafi package insert: Wilmington, DE, Incyte, 2013)	CYP3A4*			No	Not studied	Yes	CYP3A4 inhibitors (strong): avoid combination; if combination is necessary, reduce ruxolitinib to 10 mg twice daily; if platelets $< 100{,}000/mm^3$, avoid coadministration QTc: ruxolitinib may prolong QT interval; obtain baseline and monitor appropriately
Sorafenib (Nexavar package insert: Wayne, NJ, Bayer HealthCare, 2013)	CYP3A4*, UGAT1A9	CYP2B6++, CYP2C9++, CYP2C8+++, UGT1A1, UGT1A9		No	Yes	Yes	QTc: sorafenib may prolong QT interval; monitor appropriately Warfarin: sorafenib may elevate INR in some patients; monitor appropriately.
Sunitinib (Sutent package insert: New York, NY, Pfizer, 2013)	CYP3A4*	BCRP, P-gp		Not studied	Not studied	Yes	CYP3A4 inhibitors (strong): coadministration of sunitinib with strong CYP3A4 inhibitors may increase sunitinib concentrations; consider reducing sunitinib dose to 37.5 mg/day (GIST/RCC) or 25 mg/day (PNET) CYP3A4 inducers (strong): avoid combination; if combination necessary, consider increasing dose of sunitinib to 87.5 mg/day (GIST/RCC) or 62.5 mg/day (PNET) QTc: Sunitinib may increase QT interval; monitor appropriately
Tamoxifen (Nolvadex package insert: Wilmington, DE, AstraZeneca, 2003)	CYP2C9*, CYP2D6*, CYP3A4*, CYP2A6−, CYP2B6−, CYP2E1−	CYP2B6+, CYP2C9+, CYP3A4+, CYP2C8++, P-gp		Not studied	Yes	Not studied	Coumarin-containing products: coadministration with tamoxifen may increase anticoagulant effect; monitor PT/INR appropriately Letrozole: coadminstration of letrozole and tamoxifen results in reduction of letrozole in plasma; administer letrozole immediately after tamoxifen

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Table A1. (Continued)

Oral Oncologic	Substrate	Competitive Inhibitor	Competitive Inducer	Effect of Acid Suppression on Absorption	Warfarin Effects	QTc Prolongation	Drug-Related Considerations
Temozolomide (Temodar package insert: Whitehouse Station, NJ, Merck, 2013)				None studied	Not studied	Not studied	
Thalidomide (Thalomid package insert: Summit, NJ, Celegene, 2013)				Not studied	Not studied	Not studied	
Thioguanine (Tabloid package insert: Research Triangle Park, NC, GlaxoSmithKline, 2009)				No	Not studied	Not studied	
Topotecan (Hycamtin capsules package insert: Research Triangle Park, NC, GlaxoSmithKline, 2011)	P-gp, BCRP			No	Not studied	No	
Trametinib (Mekinist package insert: Research Triangle Park, NC, GlaxoSmithKline, 2013)				Not studied	Not studied	Not studied	No formal drug interactions have been evaluated Trametinib is not substrate of CYP enzymes, P-gp, or BCRP in vitro
Tretinoin (Vesanoid package insert: Nutley, NJ, Roche, 2008)	CYP2A6−, CYP2B6−, CYP2C9−, CYP2C8*	CYP2C9+	CYP2E1++	Not studied	Not studied	Not studied	
Vemurafenib (Zelboraf package insert: South San Francisco, CA, Genentech, 2013; Coumadin package insert: Princeton, NJ, Bristol-Myers Squibb, 2010)	CYP3A4−, P-gp	CYP1A2++, CYP2D6+, P-gp	CYP3A4++	Not studied	Yes	Yes	Anticoagulants: vemurafenib may increase anticoagulant effect; monitor therapy QTc: dose-dependent QTc prolongation with vemurafenib; monitor therapy
Vismodegib (Erivedge package insert: South San Francisco, CA, Genentech, 2012)	CYP2C9−, CYP3A4−, P-gp	CYP2C8+, CYP2C9+, CYP2C19+, BCRP+		Possible	No	No	Acid suppressors: administration of medications that alter gastric pH may reduce bioavailability of vismodegib; studies have not been done conducted to evaluate this interaction
Vandetanib (Caprelsa package insert: Wilmington, DE, AstraZeneca, 2013)	CYP3A4*	P-gp, BCRP		No	Not studied	Yes	QTc: vandetanib may prolong QT interval; torsade de pointes and sudden death reported; providers should correct electrolyte imbalance before initiating therapy (hypocalcemia, hypokalemia, hypomagnesemia); monitor electrolytes and ECG for baseline, at 2-4 weeks, at 8-12 weeks, and every 3 months; monitoring indicated at same schedule after dose reductions and with dose interruptions lasting > 2 weeks; avoid use of QT-prolonging agents; if concomitant use with QT-prolonging agents cannot be avoided, monitor ECG more frequently
Vorinostat (Zolinza package insert: Whitehouse Station, NJ, Merck, 2013)				Not studied	Yes	Yes	Coumarin-derived anticoagulants: vorinostat may increase anticoagulant effect; monitor therapy QTc: vorinostat may prolong QT interval; monitor appropriately

NOTE. * Indicates major substrate; −, minor substrate; +, weak inducer/inhibitor; ++, moderate inducer/inhibitor; and +++, strong inducer/inhibitor.
Abbreviations: AUC, area under the curve; BCRP, breast cancer resistance protein; CYP, cytochrome; ECG, electrocardiogram; GIST, GI stromal tumor; H2, histamine 2; H2RA, histamine 2-receptor antagonist; HER2, human epidermal growth factor receptor 2; INR, international normalized ratio; LMWH, low–molecular weight heparin; MAOI, monoamine oxidase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; P-gp, P-glycoprotein; PT, prothrombin time; PNET, primitive neuroectodermal tumor; RCC, renal cell carcinoma; TCA, tricyclic antidepressant.