Clinically Relevant Drug Interactions in the Cancer Setting

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Abstract

Along with the fast pace of oncology drug approvals is the heightened opportunity for drug-drug, drug-food, and drug-herbal interactions. Attendees at the JADPRO Live Virtual 2021 conference learned about the pharmacodynamic and pharmacokinetic mechanisms of drug interactions and how to integrate appropriate therapeutic management strategies to optimize patient care and minimize the potential outcomes of severe drug interactions.

Recognizing clinically relevant drug interactions—drug-drug, drug-food, and drug-herbal—remains an important challenge for advanced practitioners. At JADPRO Live Virtual 2021, David DeRemer, PharmD, BCOP, FCCP, FHOPA, discussed the pharmacodynamic and pharmacokinetic mechanisms of drug interactions that are clinically relevant in cancer, and the integration of appropriate therapeutic management strategies to minimize the potential risks they pose.

Dr. DeRemer is Clinical Associate Professor and Assistant Director of Experimental Therapeutics at the University of Florida Health Cancer Center in Gainesville.

The sheer number of drugs now used in the treatment of cancer presents an opportunity for many drug interactions and calls for timely assessment of these risks by providers. "Our goals should be to minimize adverse events associated with these drug interactions and maximize clinical efficacy," he said.

Numerous risk factors can raise the potential for adverse reactions, the prime one being polypharmacy. Each additional drug is thought to raise the drug-drug interaction risk by 40%, and eight or more drugs is believed to be the cautionary threshold. Other risk factors include advanced age, multiple comorbidities (especially organ dysfunction), and certain pharmacogenomic polymorphisms. Drugs with a narrow therapeutic range, or low-end therapeutic index, such as warfarin, can be most susceptible to an interaction.

"While the potential for drug interactions may be certain, teasing out those that are clinically significant or relevant—minimizing the 'noise'—can be a challenge," Dr. DeRemer added. "It's very trying to

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identify the drugs that could significantly affect both safety and efficacy of treatment."

HOW INTERACTIONS OCCUR

Dr. DeRemer described the complex processes by which these interactions can occur. Simply put, drug disposition involves absorption, distribution, metabolism, and excretion. Drug interactions can be the result of pharmacokinetics and pharmacodynamics or a combination of these mechanisms. Pharmacodynamic interactions occur when two drugs or substances have similar molecular targets but they don't affect the pharmacokinetic parameters of each other. The result is an alteration of biochemical or physiological effects of the drug. Pharmacokinetic interactions involve one drug or substance altering the absorption, distribution, metabolism, and excretion of a drug.

Cardio-oncology—the recognition that certain drugs have adverse effects on the heart—is increasingly appreciated in this field. Many of the classic anticancer drugs, such as anthracyclines, can prolong QTc intervals, but this prolongation is frequently reported as well with tyrosine kinase inhibitors. Table 1 shows some of the drugs implicated in this toxicity.

CYTOCHROME P450 ENZYMES

The human cytochrome P450 system consists of over more than 50 enzymes that are responsible for phase I metabolism of many drugs, nutrients, endogenous substances, and environmental toxins. About half a dozen account for 90% of drug oxidation.

The CYP substrates are drugs or other substances that are metabolized by cytochrome P450 or other enzymes, including drugs or prodrugs. CYP inhibitors are substances that compete with other drugs for the CYP enzyme; this affects therapeutic response to that medication and can increase risk of toxicity. CYP inducers are substances that may increase the CYP enzyme activity, thus decreasing the substrate concentration and potentially decreasing efficacy. Strong inducers or inhibitors are associated with more than a five-fold change in area under the curve (AUC) for serum drug concentrations. Strong inhibitors can change the clearance of a medication by 80%, increasing the potential for toxicity.

Table 2 shows strong CYP3A4 inhibitors and inducers relevant to cancer; these should not be used together. Dr. DeRemer referred listeners to the FDA website for more detailed information (FDA, 2021a).

VINCRISTINE, TAMOXIFEN RECOMMENDATIONS

Dr. DeRemer cautioned listeners to be particularly watchful with vincristine, which is often used in treating leukemia and can have serious interactions with CYP3A4 inhibitors, including neurotoxicity, seizures, gastrointestinal symptoms, and electrolyte abnormalities. Such adverse effects can occur when vincristine is used with azole antifungals, macrolide antibiotics, and NK1 antagonists (aprepitant, etc).

The CYP2D6 phenotype can be a consideration for patients prescribed tamoxifen. Tamoxifen greatly reduces breast cancer recurrence risk but there is substantial variability in treatment response, some of which may be attributed to a germline genetic variation. CYP2D6 is a key enzyme in the metabolism of tamoxifen to its active metabolites, and variants in this gene have been associated with reduced tamoxifen metabolism. The National Comprehensive Cancer Network (NCCN) does not, however, recommend CYP2D6 testing, but American Society of Clinical Oncology

Table 1. Pharmacodynamic Interactions

Classification risk (incidence)	Drug
High (> 10%)	Arsenic trioxide, bosutinib, capecitabine, cediranib
Moderate (5%–10%)	Belinostat, dasatinib, lenvatinib, sorafenib, sunitinib, vandetanib
Low (1%–5%)	Imatinib, lapatinib, nilotinib, paclitaxel, panobinostat, ponatinib, vemurafenib
Very low (<1%)	Anthracyclines, afatinib, ceritinib, pazopanib, pertuzumab, trastuzumab

Note. Information from Porta-Sanchez et al. (2017); Van Leeuwen et al. (2014).

Table 2. CYP3A4 Drug-Drug Interaction Management

Recommendation	Strong 3A4 inhibitors	Strong 3A4 inducers
Contraindicated or not recommended	Abemaciclib (ketoconazole only), acalabrutinib, bosutinib, cobimetinib, crizotinib, everolimus, idelalisib, neratinib, regorafenib, sonidegib, vemurafenib	Abemaciclib, abiraterone, apalutamide, axitinib, bosutinib, cobimetinib, crizotinib, dabrafenib, duvelisib, encorafenib, fostamatinib, glasdegib, ibrutinib, idelalisib, ivosidenib, ixazomib, lorlatinib, midostaurin, neratinib, nilotinib, olaparib, osimertinib, palbociclib, panobinostat, pazopanib, ponatinib, regorafenib, ribociclib, sonidegib, sorafenib, tamoxifen, venetoclax
Avoid or monitor for adverse events	Dabrafenib, erlotinib, gilteritinib, glasdegib, midostaurin	Etoposide, mitotane

Note. DDI = drug-drug interaction. Information from Rogala et al. (2019).

(ASCO) guidelines suggest women taking tamoxifen avoid the serotonin reuptake inhibitors paroxetine and fluoxetine, which are strong CYP2D6 inhibitors that can decrease levels of tamoxifen's active metabolites (Rogala et al., 2019).

ORAL ONCOLYTICS AND ACID SUPPRESSION

Tyrokine kinase inhibitors require stomach acid for optimal absorption; therefore, drugs that reduce acid may affect their absorption. Specifically, drug-drug interactions have been noted between acid suppression agents and ceritinib (Zykadia), gefitinib (Iressa), erlotinib (Tarceva), dasatinib (Sprycel), pazopanib (Votrient), nilotinib (Tasigna), lapatinib (Tykerb), bosutinib (Bosulif), alectinib (Alecensa), sunitinib (Sutent), and tivozanib (Fotivda). The data on this are not completely consistent in terms of the clinical significance; therefore, advanced practitioners have some discretion in this area. Based on more established data in this regard for dasatinib, Dr. DeRemer cautioned against the concomitant use of dasatinib and acid suppressive agents (Eley et al., 2009).

MEMBRANE TRANSPORTERS

Membrane transporters can be major determinants of safety and efficacy. More than 400 membrane transporters are found within two major super families. ABC (ATP-Binding Cassette Transporter Family) includes multidrug resistance proteins (P-glycoprotein [P-gp], also known as MDR1 or ABCB2); and SLC (SoLute Carrier Transporter Family), one of which is organic cation transporters.

P-gp is the most evaluated multidrug resistant protein transporter associated with resistance to chemotherapy. More than 100 polymorphisms have been identified, the most studied of which is C3435T. Most P-gp inhibitors also inhibit CYP3A. Cancer drugs that are substates for P-gp are primarily vinca alkaloids, etoposide, anthracyclines, and taxanes. Noncancer agents include dabigatran, digoxin, and fexofenadine. P-gp inhibitors include amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir, ritonavir, propafenone, quinidine, ritonavir, telaprevir, and verapamil. Inhibitors of the P-glycoprotein drug efflux pump may increase the serum concentrations of drugs that are substrates of P-glycoprotein.

DIRECT ORAL ANTICOAGULANTS

Direct oral anticoagulants (DOACs), including apixaban, edoxaban, and rivaroxaban, have transformed the management of venous thromboembolism, and their use in oncology is growing. They are not only P-gp transporters but are also metabolized by CYP3A4. Clinicians should avoid the concurrent use of combined P-gp and strong CYP3A4 inhibitors/inducers, which could increase the effect of the DOACs. Tyrosine kinase inhibitors, antiemetics, and hormonal agents can fall into this category, and should not be used with DOACs, he said.

HIGH-DOSE METHOTREXATE

High-dose methotrexate is one drug for which impaired clearance can have significant adverse effects. Nonsteroidal anti-inflammatory drugs, penicillin-derivatives, probenecid, salicylates,

gemfibrozil, and sulfamethoxazole and trimethoprim (SMX-TMP) have all been associated with direct inhibition of renal excretion and should be avoided with high-dose methotrexate. Other agents to avoid are those that can decrease glomerular filtration, including amphotericin, aminoglycosides, and contrast dyes. Other interactions are possible with proton pump inhibitors, P-gp/ABCB1 inhibitors, levetiracetam, and chloral hydrate.

DRUG-FOOD INTERACTIONS

Dr. DeRemer then discussed some common interactions between cancer drugs and food. One common scenario pertains to prostate cancer treatment with abiraterone acetate, which should be taken on an empty stomach. Consumption with a high-fat meal can significantly increase the AUC and potentiate toxicities (Chi et al., 2015), he said.

Small-molecule inhibitors particularly lend themselves to food interactions. The ones shown in Table 3 have a narrow therapeutic window, so significant increases in AUC may significantly increase toxicities. The table reflects just some of the data in an exhaustive study that also describes interactions with beverages, including sodas, green tea, and others (Veerman et al., 2020).

DRUG-HERBAL INTERACTIONS

"Drug-herbal interactions have become more prominent in my own practice, as many things on patients' very long list of medications are now herbal products," he continued.

A French study of about 300 cancer patients on oral anticancer agents used software programs to analyze interactions with other drugs and herbal products (Prely et al., 2021). More than 90% of patients had at least one interaction, mostly with traditional drugs, but 25% had a drug-herbal interaction. Prospective screening identified most reactions to be with crizotinib, ibrutinib (Imbruvica), lapatinib, palbociclib (Ibrance), pazopanib, and sunitinib, which interacted with, respectively, turmeric; acai berry, ginger, psyllium; bitter orange; aloe vera; dandelion; and grapefruit. These combinations, mostly through the CYP3A4 pathway, are associated with potential decreases in absorption, increases in toxicity, and prolongation of QT interval.

TIPS FOR AVOIDING AND MANAGING INTERACTIONS

Dr. DeRemer offered some ways that might ameliorate the chances of drug-drug interactions: avoid concomitant use of medications; temporarily discontinue one of the drugs; modify the dosage of the new drug; stagger the administration (for instance, a tyrosine kinase inhibitor at night and acid-reducing agent in the morning); and implement specific monitoring strategies, such as therapeutic drug monitoring of voriconazole or tacrolimus. The main management strategy should be real-time assessment and comprehensive medication reconciliation, he said. It is critical to identify potential interactions, assess for and act on inter-

Table 3. Small-Molecule Inhibitors: Food Interactions

Inhibitor[a]	Change in C_{max} (%)	Change in AUC (%)	FDA or EMA recommendation
Alectinib	170%	192%–210%	Take with food
Bosutinib	47%–80%	54%–70%	Take with food
Ceritinib	41%	73%	Take 450 mg with food or 750 mg without food
Ibrutinib	163%–400%	62%–200%	Take with food
Lapatinib	166%–203%	100%–325%	Take without food
Nilotinib	48%–112%	43%–82%	Take without food
Pazopanib	108%	134%	Take without food
Vemurafenib	114%–150%	150%–400%	Take with or without food

Note. AUC = area under the curve; FDA = U.S. Food and Drug Administration; EMA = European Medicines Agency. Information from Veerman et al. (2020).
[a]Data represents when administered with high-fat meal.

actions that are flagged, communicate the information to the relevant providers, monitor for effects, and document everything.

FURTHER RESOURCES

Lexicomp Online and Micromedex Solutions are software programs that offer evaluation analytics that look for potential drug interactions. Product package inserts contain useful information as well, and the National Library of Medicine (2021) and the FDA (2021b) have helpful websites. For help with herbal products, the Memorial Sloan Kettering Cancer Center offers a useful website called "Herbs, Botanicals, & Other Products" (2021).

Disclosure

The presenter had no conflicts of interest to disclose.

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