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AHA SCIENTIFIC STATEMENT

Cardio-Oncology Drug Interactions: A Scientific Statement From the American Heart Association

Craig J. Beavers, PharmD, FAHA, Chair; Jo E. Rodgers, PharmD, Vice Chair; Aaron J. Bagnola, PharmD; Theresa M. Beckie, PhD, FAHA; Umberto Campia, MD, MSc, FAHA; Katherine E. Di Palo, PharmD, FAHA; Tochi M. Okwuosa, MD, FAHA; Eugene R. Przespolewski, PharmD; Susan Dent, MD; on behalf of the American Heart Association Clinical Pharmacology Committee and Cardio-Oncology Committee of the Council on Clinical Cardiology and Council on Genomic and Precision Medicine; and the Council on Peripheral Vascular Disease

ABSTRACT: In the cardio-oncology population, drug interactions are of particular importance given the complex pharmacological profile, narrow therapeutic index, and inherent risk of therapies used to manage cardiovascular disease and cancer. Drug interactions may be beneficial or detrimental to the desired therapeutic effect. Clinicians in both cardiology and oncology should be cognizant of these potential drug-drug interactions that may reduce the efficacy or safety of either cardiovascular or cancer therapies. These risks can be mitigated through increased recognition of potential drug-drug interaction, use of alternative medications when possible, and careful monitoring. This scientific statement provides clinicians with an overview of pharmacodynamic and pharmacokinetic drug-drug interactions in patients with cancer exposed to common cardiovascular and cancer medications.

Key Words: AHA Scientific Statements ■ cardiovascular system ■ drug interactions ■ medical oncology ■ pharmacokinetics ■ pharmacology

Cardio-oncology is a rapidly evolving field in which patients with cancer and cardiovascular risk or disease are exposed to complex medication regimens, placing individuals at increased risk for potential drug interactions (DIs).[1] A DI is defined as the pharmacological or clinical response to the administration or coexposure of a medication with another substance that modifies the patient's response to the medication in a beneficial or detrimental manner. DIs can cause changes in the disposition of medicines that, even if apparently small, could significantly alter their efficacy or toxicity.[2] Given the rapid pace of cancer drug development, relevant DIs may be unrecognized until widespread use occurs after market approval. Furthermore, most cardiovascular and cancer therapies tend to have complex pharmacological profiles, including intrapatient and interpatient variability, narrow therapeutic index, and a steep dose-toxicity curve.[1]

It is important to consider that other substances or factors also can affect medication disposition, including food, nutritional supplements, complementary alternative therapies, formulation excipients, and environmental factors.[3] Interpatient variability can influence a DI given the potential impact of age, sex, genetics, and comorbid conditions on drug handling.[2,3] Knowledge of the mechanism of a DI is critical to minimize adverse reactions and interactions. In select instances, medications may be combined intentionally to take advantage of a DI in a beneficial manner. The purpose of this scientific statement is to highlight common DIs that occur in concomitant cardiovascular and cancer medication therapy and to discuss considerations for management or avoidance of these interactions for the cardio-oncology population. This scientific statement is designed to give clinicians an overview of critical and common DIs and is not intended to be an exhaustive discussion of all DIs. Clinicians are encouraged to check multiple sources, including, but not limited to, medication databases, medication prescription labels, primary literature, and case reports, for additional information because of the considerable variability that exists with DI screening databases.[4,5]

TYPES OF DIs

The majority of this scientific statement focuses on the 2 primary mechanistic categories used to broadly classify

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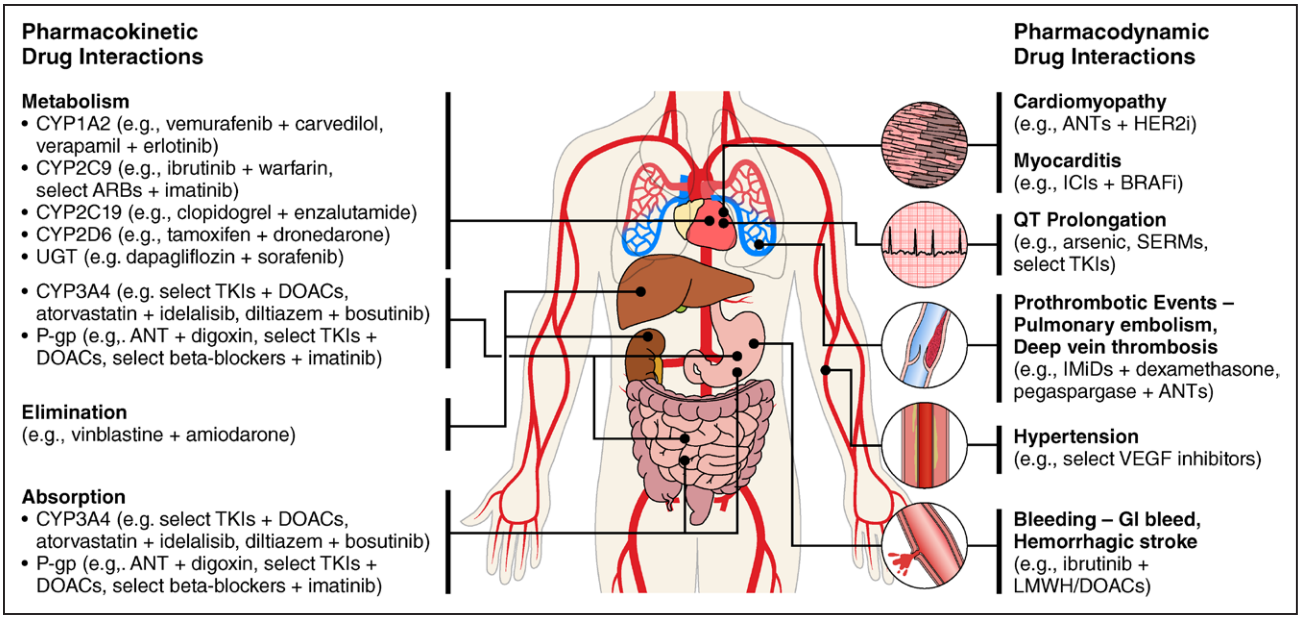

Figure. Cardio-oncology pharmacokinetics and pharmacodynamic drug interactions.
ANT indicates anthracycline; BRAFi, BRAF inhibitor; CYP, cytochrome P450; DOAC, direct acting oral anticoagulant; GI, gastrointestinal; HER2i, human epidermal growth factor receptor 2 inhibitor; ICI, immune checkpoint inhibitor; IMiD, immunomodulatory agent; LMWH, low-molecular-weight heparin; P-gp, P-glycoprotein; SERM, selective estrogen receptor modulator; TKI, tyrosine kinase inhibitor; UGT, uridine 5′-diphospho-glucuronosyltransferase; and VEGF, vascular endothelial growth factor.

DIs: pharmacodynamic interactions and pharmacokinetic interactions (Figure). A third mechanistic category is pharmaceutical interactions, which are related to physical or chemical incompatibility that may be beneficial or detrimental. However, these interactions are routinely addressed by altered formulation during manufacturing or admixture (eg, encapsulations of doxorubicin in pegylated liposomes, dilution of aldesleukin in 5% dextrose with 0.1% albumin), adjustment in medication administration (eg, administer taxane before platinum, administer 5-fluorouracil before taxane), or other considerations.[1] One pharmaceutical interaction unique to cardio-oncology occurs when the cytotoxic active ingredient paclitaxel is dissolved in a solvent mixture of polyoxyethylated castor oil and ethanol (50/50 vol/vol). The solvent increases the paclitaxel area under the curve with lower clearance and distribution volume.[1] This difference is likely attributable to entrapment of paclitaxel by the nonionic solvent, preventing distribution into tissues. Cardiotoxicity induced by anthracyclines is enhanced by concomitant use of paclitaxel, possibly because doxorubicin is modified pharmacokinetically by the paclitaxel solvent.

PHARMACODYNAMIC INTERACTIONS

A pharmacodynamic interaction occurs when the pharmacological effect of 1 medication is altered by another medication in a combination regimen. A pharmacodynamic interaction occurs when ≥2 drugs have mechanisms that result in the same physiological outcome. This type of interaction may be synergistic (the effect of 2 medications is greater than the sum of their individual effects), antagonistic (the effect of 2 medications is less than the sum of their individual effects), or additive (the effect of 2 medications is merely the sum of the effects of each). Although pharmacodynamic interactions are relatively common in clinical practice, adverse outcomes usually can be avoided or minimized if clinicians take this into consideration.[6–8]

The following sections describes pharmacodynamic interactions in patients with cancer in the context of various cardiovascular toxicities (eg, hypertension, cardiomyopathy) common to cardio-oncology. It is important to note that pharmacodynamic interactions should not be confused with iatrogenic disease (drug-induced disease), which is beyond the scope of this scientific statement.

Hypertension

Hypertension is more prevalent in patients with cancer and survivors compared with the general population and was 2.6-fold higher (95% CI 1.6–4.7) among survivors of childhood cancer compared with the general population.[9] Moreover, hypertension is the most common cardiovascular comorbidity observed in patients with cancer and is considered the foremost modifiable risk factor for adverse cardiovascular outcomes among patients with cancer and survivors.[10] Cancer therapies associated with hypertension are presented in Table 1.

Common anticancer therapies associated with hypertension include the vascular endothelial growth factor (VEGF) inhibitors with reported incidence in first-time users of 21%

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Table 1. Pharmacodynamic Interactions Between Common Chemotherapeutic and Cardiovascular Therapies and Management Recommendations

Interacting medications	Cardiovascular surveillance	Cardiovascular treatment/management	Permissive grade (1–5)
Hypertension			
Anti-VEGF TKIs*	BP monitoring†	First-line: ACE inhibitor, ARB‡ Second-line: CCBs§ Consider potassium-sparing diuretic therapy as appropriate on the basis of serum potassium levels	1
VEGF decoy receptor (VEGF trap)*			
Anti-VEGF monoclonal antibodies*			
Bruton TKI*	BP monitoring† Symptoms, ECG, cardiac monitor (eg, Holter monitor) to assess for Afib		
Abiraterone+steroids	BP monitoring†	Per hypertension guidelines‖ Use of prophylactic steroids (particularly prednisone) to avoid adrenal insufficiency	2
mTOR inhibitors+endocrine therapy	BP monitoring†	Per hypertension guidelines‖	1
NSAIDs+cancer therapies known to cause hypertension	BP monitoring† Creatinine/kidney function	Consider alternative therapy such as acetaminophen for pain and fever	4
Steroids+cancer therapies known to cause hypertension	BP monitoring† Edema and water retention	Diuretics, antihypertensives	2
Cardiomyopathy (CTRCD)			
Anthracyclines+anti-HER2 agents±taxanes±cyclophosphamide¶#	Echocardiogram with measured global longitudinal strain Cardiac markers: troponin, BNP, pro-BNP Consider cardiac MRI	β-Blocker ACE inhibitor, ARB Dexrazoxane Continuous-infusion doxorubicin Use of liposomal doxorubicin in place of regular doxorubicin Alternative anthracycline therapy when possible Dose limits	Varies according to baseline cardiovascular function and anthracycline-induced cardiotoxicity risk factors: 1. Cumulative anthracycline dose 2. Age 3. Duration of time after chemotherapy 4. Comorbid cardiac risk factors 5. Concomitant cardiotoxic chemotherapy 6. Chest wall radiation 7. Female sex 8. Echocardiographic evidence of toxicity 9. Infusion rates
Combination ICIs** Combination ICIs**+select cancer therapies	ECG, Troponin as symptomatic Consider baseline ECG, Troponin	Prompt discontinuation of therapy First line: corticosteroids Second line: tacrolimus, mycophenolate mofetil, antithymocyte globulin, infliximab Investigational agents: abatacept, tofacitinib[11]	3
Thrombosis			
IMiDs+dexamethasone±doxorubicin	CBC Doppler scan as symptomatic CT scan as symptomatic	Prophylaxis: LMWH in NDMM or multiple VTE risk factors Low-dose aspirin for others Treatment: LMWH	1
Pegaspargase+oral contraceptives	CBC Doppler scan as symptomatic CT scan as symptomatic	Discontinue oral contraceptives, use alternative methods of contraception	4
Pegaspargase+prednisone±doxorubicin	CBC APTT, INR, AT and fibrinogen level before initiation, and repeat as needed Doppler scan as symptomatic CT scan as symptomatic	Prophylaxis: If AT <60%–70%, thrombin infusions to AT 60%–70%, LMWH prophylaxis while hospitalized If AT >60%–70%, LMHW prophylaxis while hospitalized	1 Induction regimens with dexamethasone carry lower risk
Ponatinib+dexamethasone± doxorubicin	CBC Doppler scan as symptomatic CT scan as symptomatic	Prophylaxis: LMWH while hospitalized Low-dose aspirin	1

(*Continued*)

Table 1. Continued

Interacting medications in combination	Cardiovascular surveillance	Cardiovascular treatment/management	Permissive grade (1–5)
Bleeding			
Select VEGF inhibitors+cancer therapies known to cause bleeding or thrombocytopenia	CBC	Monitor symptoms or signs of bleeding	1
Select BTK inhibitors+cancer therapies known to cause bleeding or thrombocytopenia	CBC	Monitor symptoms or signs of bleeding	1
Select VEGF inhibitors+DOACs	CBC	Monitor symptoms or signs of bleeding	1
Warfarin+5-fluorouracil/capecitabine	CBC PT/INR	Monitor symptoms or signs of bleeding Increase frequency of PT/INR monitoring Consider reducing dose of warfarin Use an alternative to warfarin	4–5
Warfarin+cancer therapies known to cause bleeding or thrombocytopenia	CBC PT/INR	Monitor symptoms or signs of bleeding Increase frequency of PT/INR monitoring	Variable depending on interaction potential
Cancer therapies known to cause bleeding or thrombocytopenia±fish oil±vitamin E	CBC	Use alternatives to fish oil	4

Permissive grades 1 through 5: 1=allowed; 2 to 4=risk vs benefit; 5=contraindicated.

ACE indicates angiotensin-converting enzyme; Afib, atrial fibrillation; APTT, activated partial thromboplastin time; ARB, angiotensin receptor blocker; AT, antithrombin; BNP, brain natriuretic peptide; BP, blood pressure; CBC, complete blood count; CCB, calcium channel blocker; CT, computed tomography; CTRCD, chemotherapy-related cardiac dysfunction; DOAC, direct oral anticoagulant; ECG, electrocardiogram; ICI, immune checkpoint inhibitor; IMiD, immunomodulatory agent; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MRI, magnetic resonance imaging; mTOR, mechanistic target of rapamycin; NDMM, newly diagnosed multiple myeloma; NSAID, nonsteroidal anti-inflammatory drug; PT, prothrombin time; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; and VTE, venous thromboembolism.

*Anti-VEGF agents and TKIs are often used in combination with multiple different chemotherapy/cancer therapy protocols.

†Home and clinic.

‡Mortality benefits with anti-VEGF agents; used for its antiproteinuric effects particularly in patients with diabetes.

§Dihydropyridine CCBs, particularly amlodipine and felodipine, with less risk of drug interactions; CCBs have strongest data for BP control with anti-VEGF agents.

‖Latest multisociety hypertension guidelines.[12]

¶Particularly with high risk patients.

#Doxorubicin is the prototypical anthracycline for cardiomyopathy.

**Cause myocarditis as a form of cardiomyopathy. Risk of myocarditis greatest with combination ICIs.

to 40%.[13] Hypertension associated with VEGF inhibitors has been shown to be a marker of response to treatment and usually occurs as a result of VEGF inhibitor effects on vascular regression, vasoconstrictor levels, and renal parenchyma through decreased endothelial nitric oxide production.[14] Combinations of medication classes that singularly cause hypertension, discussed below, often occur within chemotherapeutic regimens and lead to a synergistic increase in blood pressure (BP) during therapy (Table 1).

BP control during use of VEGF inhibitors, alone or in combination, has been associated with overall improved cancer prognosis as well as cardiovascular prognosis and outcomes.[15] Recommendations for agents best used in the management of hypertension for patients receiving VEGF inhibitors are controversial. Preclinical experiments in rats have shown an inability of angiotensin-converting enzyme (ACE) inhibitors to modulate high increases in BP induced by VEGF inhibition likely attributable to downregulation of the renin-angiotensin-aldosterone system.[14,16] Hence, ACE inhibitors are suggested to be effective in the treatment of only mild increases in BP (10–15 mm Hg) with VEGF inhibition.[16] Nonetheless, ACE inhibitors are considered first-line agents for the management of anti–VEGF-induced hypertension primarily for their renoprotective effects (particularly in people with diabetes) given the higher risk of proteinuria on VEGF inhibition therapy.[17,18] Furthermore, studies have demonstrated that angiotensin II receptor expression strongly correlates with tumor aggressiveness and decreased survival.[19] Indeed, a meta-analysis comparing the use of ACE inhibitors or angiotensin receptor blockers in patients with cancer (4964 patients, 11 trials; urothelial, breast, hepatocellular, renal, pancreatic, prostate, non–small-cell lung, colorectal cancers) showed that the use of ACE inhibitors or angiotensin receptor blockers resulted in a significant improvement in disease-free survival (hazard ratio, 0.60 [95% CI, 0.41–0.87]) and overall survival (hazard ratio, 0.75 [95% CI, 0.57–0.99]).[20]

Clinical studies have shown more effective BP management with dihydropyridine calcium channel blockers (CCBs) after treatment with bevacizumab, and a study demonstrated greater reduction in BP with the use of CCBs and potassium-sparing diuretic agents for the management of anti–VEGF-induced hypertension with tyrosine kinase inhibitors (TKIs) in patients with renal cell cancer.[13,21] Long-acting nitrates that increase nitric oxide bioavailability also are effective in controlling hypertension associated with antiangiogenic therapy that is refractory to ACE inhibitors and CCBs.[22] However, there is a potential risk of compromising antiangiogenic benefits of the VEGF inhibitors because preclinical evidence

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suggests the role of endothelial nitric oxide production for VEGF-associated angiogenesis.[23]

Abiraterone acetate, the prodrug of abiraterone, is a selective inhibitor of androgen biosynthesis used in the treatment of prostate cancer.[24] It potently blocks cytochrome P450c17, a critical enzyme in testosterone synthesis, and is used in combination with prednisone to mitigate adverse events related to mineralocorticoid excess and secondary hyperaldosteronism such as hypokalemia, hypertension, and fluid overload.[24,25] Clinical trials have noted that hypertension is a side effect of abiraterone with or without prednisone steroid therapy, although the incidence ranges widely from 3.3% to 36.7%.[24] Such variability is likely attributable to wide-ranging abiraterone doses and concomitant steroid therapy. In a meta-analysis evaluating the risk of hypertension in patients with cancer treated with abiraterone compared with control subjects, the authors observed a significantly higher risk of all-grade (relative risk, 1.80 [95% CI, 1.47–2.19]) and high-grade (relative risk, 2.11 [95% CI, 1.66–2.68]) hypertension. The incidence of hypertension was higher with concurrent use of prednisone 5 mg once daily compared with the twice-daily dosing (32.4% versus 16.5%), suggesting abiraterone as a more potent contributor to hypertension observed with the use of both agents.[24] Similarly, in a phase 2 multicenter study of abiraterone, the incidence of hypertension was reduced with the addition of low-dose prednisone.[25] Current recommendations are to monitor BP, to manage according to the 2017 American College of Cardiology/American Heart Association guidelines for the management of high BP, and to consider prophylactic low-dose steroids as outlined in Table 1.[10,12]

The mechanistic target of rapamycin inhibitors such as everolimus and temsirolimus are often used in combination with endocrine therapy such as aromatase inhibitors for the treatment of advanced breast cancer. Hypertension was one of the most common grade 3 to 4 adverse events, with an incidence of 10% in the phase 2 BOLERO-4 trial (Breast Cancer Trials of Oral Everolimus); the incidence of hypertension was 16.0% in the BELLE-3 trial (Buparlisib Plus Fulvestrant in Postmenopausal Women With Hormone-Receptor Positive, HER2-Negative, Advanced Breast Cancer Progressing on or after mTORi).[26,27] The hypertension effect in the latter may have been a result of the buparlisib agent itself, which is a pan–phosphoinositide 3-kinase inhibitor. Recommendations include routine monitoring of BP and management of appropriate patients according to the American College of Cardiology/American Heart Association guidelines for the management of high BP.[10,12]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are sometimes used in patients with cancer for management of associated fever, pain, and inflammation because these drugs possess antipyretic, analgesic, and anti-inflammatory properties.[28] However, NSAIDs are associated with cardiovascular complications, including hypertension, which may subsequently contribute to an elevated risk of cardiovascular events such as myocardial infarction, stroke, heart failure (HF), and renal failure.[28,29] The use of NSAIDs in the cancer population and the risk for hypertension occur frequently enough to warrant caution. All NSAIDs in doses adequate to reduce inflammation and pain can increase BP in both individuals with normotension and those with hypertension, with a wide variation in observed average rise in BPs depending on the number and type of antihypertensives in use.[30,31] Alternative agents should be used instead, and if an NSAID must be used, monitoring for hypertension should occur regularly (Table 1). Given the hepatic metabolism of most chemotherapeutic agents, alternating NSAIDs with acetaminophen is often recommended. Although high-dose steroids may be reasonable to avoid liver dysfunction in select scenarios such as granulocyte stimulating factor–induced bone pain in the setting of taxanes (eg, docetaxel, paclitaxel), steroids may also aggravate hypertension and warrant close BP monitoring.

Cardiomyopathy

Cancer therapy–related cardiac dysfunction (CTRCD), defined as a decrease in the left ventricular ejection fraction of >10 percentage points to a value <53%, specific to anthracycline therapy occurs through a number of processes, including inhibition of topoisomerase II, generation of free oxygen radicals that induce DNA damage and cell apoptosis, inhibition of cellular pathways initiating apoptosis, and DNA intercalation.[32,33] Doxorubicin is the prototypical anthracycline that raises the risk of CTRCD with systolic dysfunction and HF.[34]

Chemotherapies often administered with anthracyclines, including trastuzumab, taxanes, and cyclophosphamide, can further increase the risk of cardiotoxicity.[35] Although trastuzumab is generally well tolerated, it is associated with infrequent cardiac dysfunction, manifested most often as an asymptomatic decline in left ventricular ejection fraction.[36,37] The incidence of trastuzumab-associated cardiac dysfunction is ≈5% to 10% with a 2% to 3% incidence of HF. However, used in combination with doxorubicin, trastuzumab leads to a >7-fold increased risk of HF compared with trastuzumab therapy alone.[38]

Trastuzumab-induced cardiotoxicity has been observed most frequently with concomitant administration of anthracycline and trastuzumab.[39] In a retrospective review of the original phase 2 and 3 trastuzumab clinical trials, Seidman et al[39] reported cardiomyopathy in 27% of patients treated with concomitant trastuzumab and anthracycline plus cyclophosphamide. Therefore, it is recommended that anthracyclines and trastuzumab be administered sequentially to reduce the risk of cardiomyopathy.[40] In the early-stage breast cancer setting, long-term follow-up of human epidermal

growth factor receptor 2 (HER2)–targeted trials, with sequential or non–anthracycline-containing trastuzumab regimens (eg, docetaxel, carboplatin, trastuzumab), has demonstrated the safety of this approach, with low rates of HF over time.[11] Dual HER2 blockade with trastuzumab and pertuzumab–based therapy (eg, docetaxel, carboplatin, trastuzumab+pertuzumab) has been shown to have superior clinical efficacy compared with trastuzumab-based therapy and is now considered the standard of care in the neoadjuvant and adjuvant settings.[41,42] It is important to note that dual HER2 blockade has not been associated with an increased risk of cardiotoxicity over time.[11] Indeed, this risk of CTRCD was substantially lower in patients receiving paclitaxel and trastuzumab (13%) or trastuzumab alone (3% to 7%); however, most of these patients had received prior anthracycline therapy. As previously described, taxanes reduce the metabolism of anthracyclines, leading to increased concentration of the anthracyclines.[43] An anthracycline dose of 420 mg/m^2 when combined with paclitaxel had an incidence of up to 50% for HF compared with a 5.4% rate at a dose of <360 m/m^2 anthracycline. The risk of cardiotoxicity is modestly increased when anthracyclines are combined with cyclophosphamide compared with taxanes or trastuzumab-anthracycline combinations, although, as described above, clinical trials suggest that the risk of cardiomyopathy is greatest in patients receiving concomitant trastuzumab and anthracycline plus cyclophosphamide.[39]

Several risk factors can increase risk of anthracycline toxicity, as presented in Table 1. Increased cumulative dose of anthracyclines amplifies this pharmacodynamic DI. Farolfi et al[44] showed that a previous cumulative dose >240 mg/m^2 doxorubicin or >500 mg/m^2 epirubicin increased the risk of trastuzumab-induced cardiotoxicity 3-fold compared with lower doses. Similarly, Cochet and colleagues[45] stratified patients on the basis of epirubicin doses of 0, 300, and 600 mg/m^2 and found that trastuzumab-induced cardiotoxicity was apparent in 9% of patients without any epirubicin exposure versus a 35% prevalence in patients exposed to 600 mg/m^2 epirubicin. Recent position statements and guidelines consider individuals exposed to a cumulative dose of doxorubicin 250 mg/m^2 or its equivalent to be at higher risk of developing CTRCD.[40,46]

Dexrazoxane, an iron chelator and topoisomerase inhibitor, has been shown to be effective in preventing anthracycline-induced cardiotoxicity,[47] particularly in children.[35] It is currently approved by the US Food and Drug Administration for use in patients with metastatic breast cancer who have received doxorubicin doses of >300 mg/m^2 and who will continue to receive doxorubicin to maintain tumor control; other uses are considered off-label.[48] Other prophylactic measures that have been considered include the use of liposomal doxorubicin, longer infusions of doxorubicin infusion (eg, >96 hours), and use of other anthracycline agents such as epirubicin or anthracycline-like agents such as mitoxantrone rather than doxorubicin.[35] These strategies are not always practical (eg, need for central lines with longer infusions), and the drug substitutions may not always be as efficacious in specific disease settings. Select standard HF agents, including ACE inhibitors and β-blockers, have shown some promise in the prevention of CTRCD but routine guidelines should be followed once HF has occurred.[49]

Myocarditis

Although immune checkpoint inhibitors (ICIs) also have been associated with cardiomyopathy, myocarditis has recently been recognized as the more injurious CTRCD associated with ICI use. ICIs have become the cornerstone for treatment of advanced malignancies and have led to long-term tumor responses and improved survival.[50,51] These monoclonal antibodies block important immune checkpoint molecules such as programmed cell death ligand 1, PD-1 (programmed cell death protein 1), and cytotoxic T lymphocyte-associated antigen-4. Although ICIs lead to cell-mediated cytotoxicity resulting from removal of the mechanism that keeps the immune system regulated, host tissues can sometimes become unintended targets of these T cells. Although rash, colitis, myositis, arthritis, and pneumonitis are some autoimmune toxicities that may occur; the heart, liver, nervous system, and kidneys also can be affected with generally more severe reactions.[52]

ICI-related myocarditis has a reported incidence of 0.04% to 1.14%, but compared with other immune-related adverse events, it has a significantly higher associated mortality of 25% to 50%.[50–52] In addition, the use of combination ICI therapy has almost twice the incidence of myocarditis, although it is still an uncommon adverse event compared with other immune-related adverse events.[53]

The first ICI (ipilimumab, an anti–cytotoxic T lymphocyte-associated antigen-4) was approved by the US Food and Drug Administration in 2011, followed by approval of other ICIs (the PD-1 inhibitors nivolumab and pembrolizumab) in 2014.[51] Since then, ICIs (including programmed cell death ligand 1 inhibitors such as atezolizumab and avelumab) have been studied as combination therapy for various malignancies. Combination ICI therapy (anti–cytotoxic T lymphocyte-associated antigen-4 in conjunction with anti–PD-1 therapy) appears to portend a 4.7-fold increased risk of developing myocarditis compared with single therapy.[54]

Given their complementary response profiles and synergy in generating antitumor immunity, there is a strong rationale for combining ICIs and TKIs, including BRAF and MEK inhibitors, to affect the tumor microenvironment and

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enhance tumor immunogenicity.[55–57] In fact, clinical trials of ICI with BRAF and MEK inhibition have demonstrated enhanced efficacy.[56,57] In renal cell carcinoma, the TKI axitinib and the ICI pembrolizumab are now a standard of care regimen, and similar approaches of combining TKI and ICI are being investigated in multiple other tumor types.[55,58,59] Similarly, combination treatment with chemotherapy and ICIs often is used in patients with advanced lung cancer. Such combinatorial approaches have been hypothesized to increase the susceptibility of cardiomyocytes to ICI-mediated inflammation, leading to higher rates of CTRCD. Beyond the ICI combination therapy, immune myocarditis was also reported within the first 15 days of therapy among those who received combination therapy with ICI and TKIs.[55] Furthermore, in the phase 3 study of durvalumab as a consolidation therapy after chemoradiotherapy in patients with stage 3 non–small-cell lung cancer, cardiac adverse events were reported in 4.4% of patients.[60] However, registration trials for pembrolizumab plus chemotherapy (pemetrexed and a platinum-based drug) in metastatic non–small-cell lung cancer or for squamous non–small-cell lung cancer (carboplatin and paclitaxel/derivatives) did not demonstrate increased CTRCD.[61,62] Monitoring and management recommendations are outlined in Table 1.

Prothrombotic Events

Patients with cancer have a 4-fold risk of venous thromboembolism (VTE), and active treatment with chemotherapy increases risk to 6.5-fold.[63,64] Cancer-associated VTE risk assessments such as the Khorana Score are used to help guide practitioners to identify at-risk patients.[63,65–67] The Khorana score in particular concludes that cancer type, pretreatment blood counts, and high body mass index all contribute to VTE associated with chemotherapy initiation.[63] In addition, many cancer regimens have prothrombotic properties. Drugs such as tamoxifen and cisplatin, anti-VEGF agents such as bevacizumab, and others have been shown to increase the risk of either venous or arterial thrombosis in the settings in which they are commonly used.[64,68] Understanding the potential for enhanced risk with combined use of select medications is critical because it represents a significant source of added VTE risk and morbidity and mortality.

Thromboembolic Events in the Management of Myeloma

There is a prothrombotic relationship with multiple myeloma and VTE, resulting in the SAVED (surgery within 90 days, Asian race, VTE history, age ≥80 years, and dexamethasone dose) and IMPEDE VTE (immunomodulatory agent; body mass index ≥25 kg/m^2; pelvic, hip, or femur fracture; erythropoietin stimulating agent; dexamethasone/doxorubicin; Asian Race; VTE history; tunneled line/central venous catheter; existing thromboprophylaxis) risk assessment scoring systems.[66,67] The IMPEDE VTE score is useful in identifying patients with newly diagnosed multiple myeloma at high risk for developing VTEs. The SAVED score specifically evaluates the risk associated with immunomodulatory drugs (IMiDs; thalidomide, lenalidomide, pomalidomide). These assessments link several medication-related factors to VTE, including the use of dexamethasone dose per cycle, doxorubicin, erythroid-stimulating agents, and additional risk factors. Although lenalidomide alone has minor thrombogenic activity (4%), when combined with dexamethasone, risk can increase significantly.[69,70] Although the exact interaction is not fully elucidated, it is hypothesized that corticosteroids sensitize cells to the effects of IMiDs, leading to the release of thrombogenic cytokines such as tissue factor, von Willebrand factor, and factor VIII.[70,71] Similar prothrombotic effects also are seen with other IMiDs.

The VTE risk with IMiDs and dexamethasone is dose dependent (Table 1). Compared with lower cumulative doses per cycle, cumulative dexamethasone doses of at least 480 mg per cycle (high-dose dexamethasone) have a higher risk of VTE.[69] Although the high-dose dexamethasone strategy has fallen out of favor because of worsened survival, newer analyses show that even doses of 160 mg per cycle have heightened risk, especially in patients with newly diagnosed multiple myeloma, attributable to high disease burden.[67] Low-dose aspirin is commonly coprescribed with IMiDs. However, in a meta-analysis evaluating patients with newly diagnosed multiple myeloma, low-molecular-weight heparin (LMWH) prophylaxis significantly reduced VTE risk compared with aspirin.[72] Although this did not result in a survival advantage, patients with newly diagnosed multiple myeloma should be treated with LMWH prophylaxis, and patients who are at heightened risk of bleeding, those in maintenance, and those with relapsed disease are candidates for low-dose aspirin.

Thromboembolic Events in the Management of Leukemia

Another agent commonly associated with VTE is pegaspargase.[73] Pegaspargase is used mostly to treat acute lymphocytic leukemia in adults and in children by depletion of L-asparagine and glutamine selectively in leukemic cells. Although pegaspargase has been linked to both bleeding and thrombotic events, it contributes to a prothrombotic environment by decreasing protein C, protein S, and antithrombin; activation of platelets through sensitization to adenosine diphosphate; endothelial activation; and a decline in plasminogen.[73–76] Rates of VTE associated with pegaspargase vary according to the meta-analysis, but most events occur in the central nervous system or are associated with venous catheters.[74,76] Although adult patients and those with T-cell acute lymphocytic leukemia are more likely to have thromboses, pediatric patients are more likely to develop cerebral VTE.[74,76]

Several drug-associated factors increase pegaspargase-associated thromboses.[73,74] This risk is highest during induction chemotherapy attributable to the use of anthracyclines and concomitant steroids (Table 1).[73–75]

The use of prednisone over dexamethasone accounted for a higher risk for VTE with pegaspargase during induction chemotherapy. For this reason, dexamethasone is the preferred steroid during induction in all patients. Oral contraceptives also can increase the risk for VTE with pegaspargase and should be discontinued and replaced with alternative contraceptive methods.[73] Alternative contraceptive methods should be used throughout induction at minimum and in other courses of therapy in which pegaspargase is used. Anthracyclines contribute to thromboses by increasing thrombin generation through tissue factor activity and phosphatidylserine exposure.[77]

Pediatric patients can receive enoxaparin prophylaxis (0.75–1.2 $mg \cdot kg^{-1} \cdot d^{-1}$) with antithrombin (goal antithrombin >50%) as an effective form of prophylaxis.[75] Adults initiated on pegaspargase should have activated partial thromboplastin time, international normalized ratio, antithrombin, and fibrinogen levels evaluated before initiation. For adults who are antithrombin deficient, thrombin infusions to keep antithrombin >60% to 70% and LMWH may be effective as prophylaxis.[73,75] Treatment of VTE should include holding pegaspargase with appropriate anticoagulation and antithrombin supplementation as indicated. For bleeding events, fresh-frozen plasma should be avoided because it may counteract the activity of pegaspargase given that it contains asparagine. Conservative management when correcting for hypofibrinogenemia (<50 mg/dL) with cryoprecipitate is preferred.[73]

Ponatinib is associated with a high risk of arterial thromboses attributable to its multikinase activity involving VEGF and platelet-derived growth factor receptor.[78] In addition, ponatinib can be used in combination with pegaspargase, anthracyclines, and corticosteroids in the management of acute lymphocytic leukemia, which further increases the risk for thrombotic events through complementary mechanisms.[79] Ponatinib was briefly removed from the market because of the risk of arterial thromboses. However, when it returned, the US Food and Drug Administration recommended that patients should receive concomitant low-dose aspirin.[80] An Italian retrospective showed that patients treated with aspirin prophylaxis had a lower risk of arterial thromboses.[81] For these reasons, patients should receive aspirin prophylaxis and inpatients on ponatinib should receive LMWH because of multiple VTE risk factors.[82] Last, as a result of prolonged myelosuppression in patients undergoing acute lymphocytic leukemia therapy, antifungal therapy may be indicated. Caution is warranted in the selection of antifungal agent because concurrent use of select antifungal agents with ponatinib may increase ponatinib concentrations through a pharmacokinetic interaction, potentiating a theoretical increased thrombotic risk.[83]

Bleeding

Bleeding presents a challenge for patients with advanced cancer, with at least 1 episode of bleeding occurring in ≈10% of all patients with cancer and almost 30% of patients with hematologic malignancy.[84] Bleeding can occur at any site of the body, including areas unafflicted by malignant pathology. Bleeding can be caused or exacerbated by a variety of mechanisms, including chemotherapy, NSAIDs, and other concomitant therapies. The risk of bleeding can be heightened by thrombocytopenia in patients with solid tumors involving the marrow and hematologic malignancies with intensive myelosuppressive chemotherapy regimens. Balancing the competing risks of clotting and bleeding in the patients with cancer is challenging given that cancer-associated thrombosis requires anticoagulation despite the multimodal risks for bleeding (Table 1).[85] Compared with age-matched control subjects, patients with cancer have an increased risk of bleeding when treated with anticoagulation.[86] Regardless, anticoagulants such as LMWH and select direct oral anticoagulants (DOACs) are indicated in the treatment of most patients with cancer-related thrombosis.[64,68,86]

The monoclonal antibody VEGF inhibitor bevacizumab targets VEGF, a key regulator of angiogenesis. When administered with chemotherapy, bevacizumab has been shown to improve clinical outcomes in various advanced solid tumors but is associated with an increased risk of bleeding.[87] Although bleeding is usually minor (eg, epistaxis), severe (greater than grade 3) bleeding has been reported. The reported incidence of severe pulmonary hemorrhage in 2 large phase 2 non–small-cell lung cancer trials was 1.9% and 1.2% and was more common in those with squamous histology.[87] In non–small-cell lung cancer and other tumor types, small increases in the incidence of severe nonpulmonary bleeding have been reported, primarily in the gastrointestinal or genitourinary tract and central nervous system.[87] Management includes close monitoring for signs of bleeding when used in combination with other chemotherapy agents that have bleeding risk or with agents with the propensity to induce bleeding.

Ibrutinib, an irreversible inhibitor of the Bruton tyrosine kinase, is an effective therapy in the treatment of multiple B-cell–mediated lymphoproliferative disorders but is associated with an increased risk of bleeding.[88] This has been attributed largely to the platelet-specific effects of inhibiting the nonreceptor tyrosine kinases Btk and Tec, as well as drug-induced thrombocytopenia. Off-target inhibition of Src, which has a role in platelet adhesion to collagen, also has been implicated in ibrutinib-associated bleeding.[84,88,89] The clinical impact on impaired platelet function and bleeding has not been observed with other Bruton tyrosine kinase (eg, acalabrutinib and evobrutinib).[84,89] Most bleeding events are low grade and include subcutaneous or mucosal bleeding. Major hemorrhage has been reported, with rates varying from 4% to 8% in trials that followed up patients for >1 year, with fatal hemorrhage occurring in <1% of patients.[88] Several factors may explain the variability of reported bleeding

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events, including differences in dosing, disease type, and use of other antiplatelet agents. Given the association of ibrutinib with thrombocytopenia and increased bleeding risk, any medications known to reduce platelet count should be avoided to further minimize bleeding risk.[88] Although aspirin, adenosine diphosphate receptor antagonists (eg, clopidogrel), and glycoprotein IIb/IIIa inhibitors (eg, eptifibatide) are well-known prototypes of antiplatelet drugs, other widely used agents such as NSAIDs, select antibiotics, and select psychotropic agents also can impair platelet function, although less commonly. Although rare select cardiovascular medications, including anticoagulants and antifibrinolytics, also can impair platelet function, select chemotherapeutic agents more routinely cause thrombocytopenia.[90]

Ibrutinib is commonly associated with atrial fibrillation, which often mandates anticoagulation, leading to complex decision with regard to clotting versus bleeding risk. A systemic review by Ganatra and colleagues[91] found an incidence of atrial fibrillation ranging from 3.5% to 16% across 16 studies, or a rate of 5.8 per 100 person-years. However, newer-generation Bruton TKIs have shown lower rates of arrhythmias (eg, acalabrutinib).[92] In a recent meta-analysis of 8 randomized clinical trials comprising 2580 patients, the pooled estimate showed that ibrutinib resulted in a relative risk of 4.69 (95% CI, 2.17–7.64; $P<0.001$) for developing atrial fibrillation.[93] Patients who develop atrial fibrillation on Bruton TKIs should follow algorithms similar to those used for the general population, including anticoagulation. However, special consideration should be given to balancing thrombotic risk and reducing bleeding, including avoiding unique drug-drug interactions that may coexist with certain cancer therapeutics and anticoagulants.[92]

Anticoagulant and antiplatelet agents are a common source of major bleeding events in patients with cancer. In a cohort of patients with cancer from a database of 26 US health care organizations, bleeding incidence was higher in patients with cancer compared with patients without cancer across all anticoagulants studied.[86] Although a recent meta-analysis of DOACs to treat cancer-associated thrombosis reported a lower 6-month recurrent VTE rate with DOACs compared with LMWH, DOAC use resulted in a higher rate of major bleeding and a higher rate of clinically relevant nonmajor bleeding compared with LMWH, particularly in gastrointestinal malignancy, including esophageal cancer.[94] For this reason, DOACs should be avoided in gastrointestinal tract malignancy. However, in nongastrointestinal malignancies, DOACs appear to be safe. In a recent study of patients with cancer-associated thrombosis, apixaban was found to be noninferior to subcutaneous dalteparin without increased risk of major bleeding (3.8% versus 4.0%, respectively).[95]

In addition, patients with primary or metastatic gastrointestinal malignancies and established VTE should be offered anticoagulation as described for other patients with cancer; however, there is uncertainty about agent selection and patients most likely to benefit. Some expert opinion favors LWMH at times given the improved efficacy compared with warfarin, limited drug-drug interactions, and no monitoring. However, DOAC use is slowly gaining limited evidence in this population and may be cautiously considered for patients who desire an oral option. This does not include those with active or recent gastrointestinal bleeding. It is notable that there are limited safety data for DOAC use in patients requiring cancer surgery and in those with primary central nervous system malignancies or untreated brain metastases.[96,97] In addition, there are limited data on safety in patients with cancer who have impaired renal function, obesity, thrombocytopenia, and hematologic cancers.[98]

DOACs are administered in fixed doses and have fewer DIs compared with warfarin, but like warfarin, DOACs are still subject to DIs involving altered plasma concentrations that may increase bleeding or reduce efficacy.[99] DOACs have been shown to cause fewer bleeding events than warfarin in multiple phase 3 clinical trials.[99] They are a safer class of anticoagulant to combine with a number of cancer therapies, including ibrutinib; however, there are still potential DIs with this class of anticoagulants (eg, dabigatran). If DOACs are used, some experts consider recommending dose reductions for the first 7 to 10 days despite limited evidence to support this practice.[100]

While patients with gastrointestinal malignancies maintain the most notable risk of bleeding, other risk factors for bleeding include metastatic disease, renal or hepatic disease, use of antiplatelet agents, and thrombocytopenia.[68,86] The impact of cancer therapies (eg, bevacizumab) on bleeding risk with DOACs is less well defined. In a small single-center study, patients with advanced cancer demonstrated a higher risk of bleeding events with concurrent DOACs and VEGF inhibitors compared with DOACs alone.[101] However, a recent systematic review of DIs with DOACs found that after a decade of use, the overall number of published DOAC DIs contributing to adverse events, including bleeding, is low.[99] Given that DIs with DOACs are related to multiple metabolic pathways and are relatively complex, this topic is addressed in the pharmacokinetics section.

Unlike LMWH and DOACs, warfarin is not a first-line therapy for cancer-associated VTE. However, there are occasions when warfarin may be prescribed in patients with cancer-associated thrombosis, particularly when LMWH and DOACs are not accessible.[100] Warfarin shares metabolic pathways with several cancer therapies, which may increase the risk of bleeding or decrease the efficacy of anticoagulation.[85] Although warfarin coadministration with select cytotoxic chemotherapy agents should be avoided, others require close monitoring and potential warfarin dose adjustment.

Additional details are provided in the pharmacokinetics section.

Patients with cancer may have a history of or risk factors for cardiovascular disease, including acute coronary syndromes, peripheral vascular disease, and cerebrovascular disease, which often warrant antiplatelet therapy for primary or secondary prevention.[84] Likewise, patients who experience cardiovascular events during cancer therapy may require a percutaneous coronary intervention with stenting and dual antiplatelet therapy (DAPT). Patients with cancer carry an increased risk of cardiac mortality that is not associated with ischemic events when undergoing percutaneous coronary intervention. Bleeding occurs more frequently in patients with cancer.[102] Modifying the duration of DAPT should be considered. The Society of Cardiovascular Angiography and Intervention recommends shorter duration of DAPT for patients with cancer with low platelet counts (<50 000): 2 weeks for balloon angioplasty, 4 weeks for bare metal stents, and 3 to 6 months for drug-eluting stents.[103] Of note, this consensus was published in 2016; since then, there has been increasing evidence of prescribing 1 month of DAPT and transitioning to single antiplatelet therapy in patients at high risk of bleeding.[104] In addition to enhancing bleeding risk, DIs with cancer therapies may conversely reduce the effectiveness of antiplatelet agents, which may have catastrophic implications in patients who have recently undergone percutaneous coronary intervention with stent implantation.[105] Furthermore, such patients may be at increased risk for bleeding beyond the risk for the normal population for a multitude of reasons. For example, DAPT raises the risk of major bleeding, reportedly by 40% to 50%, in patients receiving ibrutinib.[88] Thus, it is prudent to be aware of pharmacodynamic interactions involving multiple medications with an additive bleeding risk. Like oral anticoagulants, select $P2Y_{12}$ receptor inhibitors have pharmacokinetic DIs with other medications through metabolic enzymes that warrant alternative agent selection and this will be addressed in the pharmacokinetic DI section.

Arrhythmias

Cardiac arrhythmias are increasingly recognized among the cardiotoxic effects of cancer therapies.[106] Anticancer drugs may exert both on-target and off-target effects on the molecular mechanisms that regulate myocyte action potential, often leading to changes in the ECG and acute treatment-related cardiac rhythm disturbances.[107] Although a variety of types of arrhythmias may occur as an adverse effect of cancer therapies (eg, atrial fibrillation, as mentioned in the previous section), QT prolongation is more commonly associated with pharmacodynamic interactions. Of note, additive bradycardia may occur with select cancer therapies (ceritinib, crizotinib) and β-blockers, the nondihydropyridine CCBs verapamil and diltiazem, and digoxin.[107] Prolongation of the QT interval, a risk factor for torsades de pointes, is a frequent consequence of several traditional and targeted cancer therapies. A recent comparison study indicates that the Federica and Framingham formulas may provide the most accurate correction for QT interval.[108,109]

Drug-induced QT prolongation and the risk of torsades de pointes are complex phenomena affected by the presence of genetic predisposition (eg, long QT syndromes) and numerous acquired risk factors.[110] Patients with cancer may be especially vulnerable to QT prolongation because of the high prevalence of structural heart disease, chronic kidney disease, and concomitant treatments with other QT-prolonging medications or with medications involving pharmacokinetic interactions, particularly hepatic cytochrome P450 (CYP) 3A4 inhibitors. The frequent occurrence of nausea, vomiting, diarrhea, and poor oral intake, particularly during treatment, may lead to electrolyte abnormalities (eg, hypokalemia, hypomagnesemia, hypocalcemia) and acute kidney injury, which further increase the risk of QT prolongation. Hospitalized patients, particularly when critically ill, represent a high-risk population, with elevated prevalence of QTc prolongation at presentation and frequent use of non–cancer-related QT-prolonging drugs (Table 2).[111,112] To quantify the risk of QT prolongation during hospitalization, Tisdale et al[112] developed a risk score based on clinical variables independently associated with prolonged QT interval. In the validation cohort, a low score (<7) was associated with an incidence of QTc prolongation of 15% compared with an incidence of 37% and 73% in the moderate-score (7 to 10) and high-score (≥11) groups, respectively.[112] However, this risk score has not been validated in a cancer population.

Several cancer treatments have been associated with QT prolongation (Table 2). Among nontargeted therapies, arsenic trioxide is associated with the highest risk of QTc prolongation and the occurrence of torsades de pointes, with reported cases of sudden death.[113,114] Other high-risk drugs include the histone deacetylase inhibitor panobinostat and several TKIs, particularly lapatinib, nilotinib, pazopanib, sunitinib, vandetanib, and vemurafenib.[107,115–117] Ribociclib, a CDK 4/6 inhibitor approved for individuals with hormone receptor–positive HER2-negative metastatic breast cancer in combination with endocrine therapy, has been associated with an increased risk of QTc prolongation.[118] US Food and Drug Administration approval of ribociclib was contingent on close cardiac monitoring with 12-lead ECGs before initiation of treatment, at the middle of the first cycle (day 15), and before the start of cycle 2.[119] For this reason, ribociclib should be taken in the morning to further reduce risk of QTc prolongation.[119] In addition, numerous supportive care therapies used in the cancer population can result in QT prolongation (eg, antiemetics, antidepressants,

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Table 2. Drugs Associated With Prolonged QTc/Torsades de Pointes

Anticancer agents	↑ QTc	TdP	SD	FDA labeling regarding QTc
Nontargeted agents				
Arsenic trioxide	+++	++	Case reports	Boxed warning
Doxorubicin	+++	Possible	–	No statement
Histone deacetylase inhibitors			–	
Pabinostat	++	Possible	–	Boxed warning
Vorinostat	++	Possible	–	Warning and cautions
Selective estrogen receptor modulators			–	
Toremifene	++	–	–	Boxed warning
TKIs		–	–	
Ceritinib (anti ALK)	+	–	–	Warning and cautions
Crizotinib (anti-ALK)	++	–	–	Warning and cautions
Lapatinib (anti–EGFR/HER2)	+++	–	–	Warning and cautions
Nilotinib (anti–BCR-ABL)	++	+	–	Boxed warning
Pazopanib (anti-VEGFR)	++	+	–	Warning and cautions
Ribociclib (anti-CDK)	++	–	–	Warning and cautions
Sorafenib (anti–RAF/MEK)	–	–	–	Warning and cautions
Sunitinib (anti-VEGFR)	++	+	–	Warning and cautions
Vandetanib (anti-VEGF)	+++	+	–	Boxed warning
Vemurafenib (anti–RAF/MEK)	++	–	–	Warning and cautions
Nonchemotherapeutic agents with known risk of QTc prolongation/TdP				
Antiemetic and prokinetic agents: Chlorpromazine, domperidone, droperidol, ondansetron				
Antibacterial and antifungal agents: Azithromycin, chloroquine, ciprofloxacin, clarithromycin, erythromycin, fluconazole, levofloxacin, moxifloxacin, pentamidine, spiramycin				
Antiarrhythmic agents: Amiodarone, bepridil, disopyramide, dofetilide, dronedarone, flecainide, ibutilide, procainamide, quinidine, sotalol				
Psychotropic agents: Citalopram, escitalopram, haloperidol, methadone, pimozide, thioridazine				
Other agents: Cilostazol, donepezil, hydroxychloroquine				

ALK indicates anaplastic lymphoma kinase; BCR-ABL, breakpoint cluster region–Abelson; CDK, cyclin-dependent kinase; EGFR/HER2, epidermal growth factor receptor/human epidermal growth factor receptor 2; FDA, US Food and Drug Administration; MEK, mitogen-activated extracellular signal-regulated kinase; QTc, corrected QT interval; RAF, rat fibrosarcoma; SD, sudden death; TdP, torsades de pointes; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; –, data not available; +, <1%; ++, 1% to 10%; and +++, >10%.

antihistamines, antibiotics).[105] The impact of multiple medications causing QT prolongation is additive and further increases patient risk.[112] Last, numerous cancer therapies and supportive therapies are subject to pharmacokinetic interactions, which may result in increased serum concentrations, further increasing the risk of QT prolongation.

Several approaches can be used to minimize the occurrence of QTc prolongation and torsades de pointes in patients who receive QT-prolonging cancer treatments. Guiding principles include early identification of patient-related risk factors, accurate measurement of QT/QTc, correction of reversible causes of QT prolongation, awareness of pharmacodynamic and pharmacokinetic drug-drug interactions affecting QT duration, frequent monitoring during treatment, and close collaboration with the cardio-oncologist.[120,121]

PHARMACOKINETIC PRINCIPLES AND INTERACTIONS

A pharmacokinetic interaction involves 1 medication altering absorption, distribution, metabolism, or elimination of another medication. Although pharmacokinetic interactions may involve medications altering any pharmacokinetic property of another medication, the most common pharmacokinetic interactions involve metabolism.[3,6–8]

Absorption

Drug absorption is the process by which a drug enters the systemic circulation from the sites of administration. The oral route is one of the most common means of drug administration, making the stomach or small intestine the most common site for absorption.[122] Traditional chemotherapy is

administered intravenously, so the direct potential of DIs with cardiovascular pharmacotherapy is low. The emergence of novel oral cancer therapies (eg, select TKIs) and DOACs that rely on CYP3A4 or P-gp for absorption has recently increased the probability of DIs involving this route (Table 1).

Distribution

The active component of a medication is the unbound portion because it is available to reach target tissues. When medications are bound to blood components or tissue binding sites and then undergo displacement, the apparent volume of distribution theoretically will increase.[1,3] Unfortunately, the net therapeutic effect is difficult to predict because more drug is then available to either bind to its target site or undergo metabolism or renal elimination. The clinical implications of displacement of most cardiovascular and cancer medications from protein binding have been insignificant. The limited clinical significance is likely attributable to a lack of alteration in overall drug exposure. One notable exception is highly protein-bound cytotoxic therapies (eg, paclitaxel, etoposide), which have the potential to interact with other protein-bound medications such as warfarin.[1,3]

Metabolism

CYP enzymes function to metabolize potentially toxic compounds, including medications, principally in the liver. Medications, food, and herbal supplements that compete for metabolism by the same CYP enzyme or that inhibit or induce CYP enzymes produce predictable interactions from the known CYP-mediated effects of a compound. Numerous chemotherapeutic and cardiac therapies depend on or alter CYP enzymes. Although there are many enzymes in the CYP class, only a small number of enzymes are responsible for metabolism of the majority of medications (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4), with the 2 most significant enzymes being CYP3A4 and CYP2D6.[3,119,123,124]

Inhibition of CYP enzymes leads to increased substrate serum levels of the unmetabolized entity, resulting in a greater potential for toxicity. Induction leads to reduced substrate levels and the potential for reduced efficacy. As an exception, for a medication with pharmacological activity that requires biotransformation from a prodrug to an active metabolite (eg, clopidogrel), inhibition can lead to reduced efficacy and induction to increased toxicity.[2,3,125] Most DIs involving cardiovascular medications can be resolved by substituting an alternative agent within the same therapeutic class (eg, rosuvastatin substituted for simvastatin, sotalol for dofetilide) or closely monitoring serum concentrations (eg, tacrolimus).[1,105]

A drug can be metabolized by and inhibit the same enzyme, or it can be metabolized by one enzyme and inhibit another enzyme. A drug also may be metabolized by the same CYP enzyme that it induces. Certain agents such as imatinib and venetoclax are both substrates and inhibitors and can be involved in dual DIs. In addition, a medication serves as a substrate for multiple CYP enzymes (eg, warfarin) or inhibitor/inducer of multiple CYP enzymes (eg, amiodarone) (Table 3).[1,2,4,99,105,119,122–138] Furthermore, 2 drugs can competitively inhibit each other reversibly if both are substrates of the same enzyme, or 2 drugs can have a synergistic effect if both induce or inhibit the same enzyme (eg, 2 mild CYP3A4 inducers may results in moderate to strong CYP3A4 induction).[2,3,125] Venetoclax serves as an excellent example. It is metabolized by CYP3A4 and P-glycoprotein (P-gp) but also inhibits P-gp. Thus, venetoclax warrants dose reduction when administered with P-gp inhibitors (eg, carvedilol, and ranolazine) and moderate CYP3A4 inhibitors (eg, conivaptan, diltiazem), as well as dual P-gp/CYP3A4 inhibitors (eg, dronedarone, verapamil). Given that it also inhibits P-gp, concomitant use of venetoclax may increase concentrations of P-gp substrates (eg, digoxin, select DOACs, warfarin).[1–3,105,119,123,125,128,129,131]

Although CYP enzymes are responsible for roughly two-thirds of all drug metabolism, this addresses only phase 1 metabolism. One of the most important remaining enzyme families involved in phase 2 metabolism belongs to the uridine diphosphate glucuronosyltransferases (UGTs), which serve to transfer glucuronic acid to other compounds. Although a variety of cardiovascular therapies undergo UGT metabolism (eg, select sodium-glucose cotransporter-2 inhibitors, select dyslipidemic agents, losartan, dabigatran), alternative agents within the same therapeutic class can be used when a UGT inhibitor (eg, gemfibrozil, various TKIs) or inducer (apalutamide) is indicated. In general, chemotherapeutic agents undergoing UGT metabolism (eg, belinostat, irinotecan, pexidartinib, and sacituzumab govitecan-hziy) should be avoided with UGT inhibitors, and caution is advised with UGT inducers with recommendations to evaluation for loss of efficacy (Tables 3 and 4).[1,105,128,134,135] Of note, belinostat is metabolized primarily by UGT1A1, and patients with reduced activity (homozygous for the UGT1A1*28 allele) should be started with a 25% dose reduction to avoid increased toxicity.[134]

Last, both irinotecan and sacituzumab rely on UGT1A1 for glucuronidation and elimination of the active drug SN-38. Reduced UGT1A1 activity through genetic polymorphisms or drug inhibition (eg, atazanavir or gemfibrozil) increases SN-38 levels in the blood through recirculation (Table 4). This effect leads to an increase in adverse effects, including neutropenia, and use with reduced UGT1A1 activity is not recommended unless no other alternatives exist.[119,123,134,135]

Table 3 delineates cardiovascular and chemotherapeutic substrates, inducers, and inhibitors by enzyme. Of note, this table is not all encompassing. This table

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Table 3. Common Metabolic Enzymes, Substrates, Inhibitors, and Inducers in Cardiovascular and Chemotherapeutic Pharmacotherapy[1,2,4,99,105,119,122–138]

Enzyme	Drug class	Substrates	Inhibitors	Inducers
CYP1A2	Cardiovascular	Antiarrhythmic: mexiletine, lidocaine, propafenone β-Blocker: carvedilol CCB: verapamil Diuretic: triamterene	Cardiovascular agents Antiarrhythmic: mexiletine ++, propafenone + β-Blocker: propranolol + CCB: verapamil + Oncology agents Antiandrogen: abiraterone, enzalutamide BRAF kinase inhibitor: vemurafenib ++ BRM: peginterferon alfa-2b + CDK inhibitor: ribociclib + c-MET inhibitor: capmatinib ++ IDH2 inhibitor: enasidenib Multi-targeted TKI: midostaurin PARP inhibitor: rucaparib ++ VEGF TKI: axitinib, lenvatinib, pazopanib	Cardiovascular agents None Oncology agents EGFR TKI: osimertinib Multitargeted TKI: midostaurin PARP inhibitor: niraparib
	Chemotherapeutic	Angiogenesis inhibitor: pomalidomide EGFR TKI: erlotinib		
CYP2C8	Cardiovascular	Antiarrhythmic: amiodarone Anticoagulant: apixaban Loop diuretic: torsemide Soluble guanylate cyclase stimulator: riociguat	Cardiovascular agents Fibrate: gemfibrozil +++ Oncology agents Antiandrogen: enzalutamide +++ Anti-HER2 TKI: tucatinib EGFR TKI: lapatinib	Cardiovascular agents Fibrate: gemfibrozil Oncology agents Taxane: paclitaxel
	Chemotherapeutic	Alkylating agent: ifosfamide Antiandrogen: enzalutamide Anti-HER2 TKI: tucatinib RAF kinase inhibitor: dabrafenib BCR-ABL TKI: imatinib, ponatinib Taxane: paclitaxel		
CYP2C9	Cardiovascular	Anticoagulant: warfarin ARB: losartan, irbesartan, valsartan, candesartan Endothelin receptor blocker: bosentan HMGCoA reductase inhibitor: fluvastatin, rosuvastatin Loop diuretic: torsemide	Cardiovascular agents Antiarrhythmic: amiodarone ++ Antiplatelet: clopidogrel + HMGCoA reductase inhibitor: fluvastatin + Oncology agents ALK TKI: ceritinib ++ BCR-ABL TKI: imatinib + BRAF inhibitor: dabrafenib ++ c-MET inhibitor: cabozantinib + SERM: tamoxifen +++ TS inhibitor: capecitabine +, fluorouracil + Miscellaneous: teniposide +	Cardiovascular agents Endothelin receptor blocker: bosentan + Oncology agents Antiandrogen: enzalutamide ++, apalutamide +
	Chemotherapeutic	Alkylating agents: cyclophosphamide, ifosfamide BCR-ABL TKI: imatinib Proteasome inhibitor: bortezomib SERM: tamoxifen		
CYP2C19	Cardiovascular	Antiplatelet: clopidogrel β-Blocker: propranolol	Cardiovascular agents None Oncology agents Aromatase inhibitor: letrozole + c-MET inhibitor: cabozantinib +	Cardiovascular agents None Oncology agents Antiandrogen: enzalutamide ++, apalutamide ++ Steroid: prednisone +
	Chemotherapeutic	Alkylating agents: cyclophosphamide, ifosfamide BCR-ABL TKI: imatinib HDAC inhibitor: romidepsin Proteasome inhibitor: bortezomib SERM: tamoxifen Miscellaneous: teniposide, thalidomide		
CYP2D6	Cardiovascular	Antiarrhythmic: flecainide, propafenone β-Blocker: carvedilol, metoprolol, propranolol, nebivolol	Cardiovascular agents Antiarrhythmic: amiodarone +, dronedarone ++, propafenone +, quinidine +++ β-Blocker: labetalol + CCB: diltiazem +, verapamil +, felodipine+ Vasodilator: hydralazine +	Cardiovascular agents None Oncology agents None

(*Continued*)

Table 3. Continued

Enzyme	Drug class	Substrates	Inhibitors	Inducers
	Chemotherapeutic	Anthracycline: doxorubicin SERM: tamoxifen EGFR TKI: gefitinib	Oncology agents Antiandrogen: abiraterone ++, bicalutamide, enzalutamide BCR-ABL TKI: imatinib +, nilotinib BRAF kinase inhibitor: vemurafenib + BRM: peginterferon alfa-2b + EGFR TKI: gefitinib +, dacomitinib +++ HDAC inhibitor: panobinostat ++ IDH2 inhibitor: enasidenib JAK2-selective inhibitor: fedratinib ++ MEK inhibitor: cobimetinib Multitargeted TKI: midostaurin PARP inhibitor: rucaparib VEGF TKI: lenvatinib, pazopanib +, sorafenib, M-2 (active metabolite of regorafenib)	Cardiovascular agents None Oncology agents None
CYP3A4	Cardiovascular	Aldosterone receptor antagonist: eplerenone Antiarrhythmic: amiodarone, dronedarone, dofetilide Anticoagulant: apixaban, rivaroxaban, edoxaban (minimal, <4%), warfarin Antiplatelet: ticagrelor CCB: amlodipine, felodipine HMGCoA reductase inhibitor: atorvastatin, lovastatin, simvastatin mTOR inhibitor: sirolimus, tacrolimus PDE5 inhibitor: sildenafil, tadalafil SERM: tamoxifen Vasopressin antagonist: conivaptan, tolvaptan Miscellaneous: colchicine	Cardiovascular agents Antiarrhythmic: amiodarone +, dronedarone ++ Antiplatelet: ticagrelor + CCB: amlodipine +, diltiazem +++, verapamil +++ HMGCoA reductase inhibitor: atorvastatin* I_{Na} inhibitor: ranolazine + Vasopressin antagonist: conivaptan ++ Oncology agents ALK TKI: ceritinib Anti-HER2 TKI: tucatinib BCR-ABL TKI: dasatinib +, imatinib ++, nilotinib + BRAF inhibitor: encorafenib CDK inhibitor: palbociclib +, ribociclib c-MET inhibitor: capmatinib EGFR TKI: erlotinib, gefitinib, lapatinib + HDAC inhibitor: panobinostat + Antiandrogen: abiraterone +, bicalutamide + Other protein kinase inhibitor: ruxolitinib PARP inhibitor: rucaparib + PI3Kδ inhibitor: idelalisib +++ ROS1/Trk inhibitor: entrectinib + Trk inhibitor: larotrectinib	Cardiovascular agents Bosentan ++ Oncology agents ALK TKI: brigatinib, lorlatinib Antiandrogen: apalutamide +++, enzalutamide +++, mitotane +++ Anti-HER2 TKI: tucatinib BRAF inhibitor: dabrafenib +++, encorafenib, vemurafenib +++
	Chemotherapeutic	AKL TKI: brigatinib, ceritinib crizontinib, lorlatinib ANT: etoposide Antiandrogen: abiraterone, apalutamide, enzalutamide, mitotane Anti-HER2 TKI: tucatinib Aromatase inhibitor: exemestane BCL-2 protein inhibitor: venetoclax BCR-ABL TKI: bosutinib, dasatinib, imatinib, nilotinib, ponatinib BRAF inhibitor: dabrafenib, encorafenib, vemurafenib BTK inhibitor: acalabrutinib, ibrutinib c-MET inhibitor: cabozantinib CDK inhibitor: abemaciclib, palbociclib, ribociclib EGFR TKI: erlotinib, gefitinib, lapatinib, neratinib, osimertinib EGFR/VEGF TKI: vandetanib FLT3 inhibitor: gilteritinib HDAC inhibitor: panobinostat Hedgehog pathway inhibitor: glasdegib, sonidegib IDH1 inhibitor: ivosidenib MEK inhibitor: cobimetinib Multitargeted TKI: midostaurin Other protein kinase inhibitor: everolimus PARP inhibitor: olaparib		

(*Continued*)

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Table 3. Continued

Enzyme	Drug class	Substrates	Inhibitors	Inducers
		PI3Kδ inhibitor: duvelisib, idelalisib Proteasome inhibitor: ixazomib SERM: tamoxifen, toremifene TKI: fostamatinib Trk inhibitor: larotrectinib TS inhibitor: capecitabine VEGF TKI: axitinib, pazopanib, regorafenib, sorafenib, sunitinib Miscellaneous: thalidomide		
P-gp/ ABCB1	Cardiovascular	Anticoagulant: apixaban (minimal), dabigatran, edoxaban, rivaroxaban, warfarin ARB: losartan β-Blocker: labetalol, propranolol HMGCoA reductase inhibitor: atorvastatin Calcium channel blocker: diltiazem, verapamil Na+/K+ ATPase: digoxin Renin inhibitor: aliskiren	Cardiovascular agents Antiarrhythmic: amiodarone +++, dronedarone +++, propafenone, Antiplatelet: ticagrelor β-Blocker: carvedilol +++ CCB: verapamil +++, diltiazem, nicardipine +++, felodipine + HMGCoA reductase inhibitor: atorvastatin I_{Na} inhibitor: ranolazine	Cardiovascular agents None Oncology agents ANT: doxorubicin
	Chemotherapeutic	Alkaloid: irinotecan, topotecan ANT: daunorubicin, doxorubicin, etoposide Antimicrotubule: paclitaxel, vinblastine, vincristine EGFR TKI: lapatinib	Oncology agents ALK TKI: alectinib Anti-HER2 TKI: tucatinib BCL-2 protein inhibitor: venetoclax CDK inhibitor: abemaciclib, palbociclib c-MET inhibitor: capmatinib EGFR TKI: afatinib, erlotinib, gefitinib, lapatinib FGFR inhibitor: pemigatinib VEGF TKI: sorafenib, sunitinib	
UGTs	Cardiovascular	UGT1A1: Cholesterol absorption inhibitor: ezetimibe UGT1A9: Anticoagulant: dabigatran SGLT2 inhibitor: canagliflozin, dapagliflozin IMPDH inhibitor: mycophenolate mofetil UGT2B7: Angiotensin receptor blocker: losartan Cholesterol absorption inhibitor: ezetimibe HMGCoA reductase inhibitor: lovastatin, simvastatin Miscellaneous: gemfibrozil	Cardiovascular agents UGT1A1: gemfibrozil Oncology agents UGT1A: ALK TKI: lorlatinib +++ UGT1A1: BCL-2 protein inhibitor: venetoclax BCR-ABL TKI: nilotinib BRAF inhibitor: encorafenib EGFR TKI: dacomitinib, erlotinib IDH2 inhibitor: enasidenib PARP inhibitor: rucaparib, olaparib PI3Kδ inhibitor: idelalisib TKI: fostamatinib, pexidartinib VEGF TKI: lenvatinib, pazopanib, regorafenib +++, sorafenib UGT1A4: VEGF TKI: lenvatinib UGT1A9: VEGF TKI: lenvatinib, sorafenib	Cardiovascular agents None Oncology agents UGT: Antiandrogen: apalutamide
	Chemotherapeutic	UGT1A1: HDAC inhibitor: belinostat Topo-I inhibitor: SN-38 (active metabolite of irinotecan) Topo-II inhibitor: etoposide UGT1A4: TKI: pexidartinib UGT1A9: Topo-I inhibitor: SN-38 (active metabolite of irinotecan) VEGF TKI: regorafenib, sorafenib		

This table was prepared to provide examples of index substrates and inhibitors/inducers and is not intended to be an exhaustive list. In addition, the sensitivity of the inhibitor/inducer (eg, mild, moderate, strong) is not specified for every agent given the lack of availability or complexity of this information. Most medications are categorized only under the enzyme for which they predominantly serve as a substrate or inhibitor/inducer and are not listed multiple times if they serve as such for multiple enzymes.

(*Continued*)

While substrates may also be indexed as sensitive and moderately sensitive, given the complexity of interactions this information is not detailed.

+++Strong inhibitor/inducer: increase the area under the curve of sensitive index substrates of a given metabolic pathway ≥5-fold. Select strong inhibitors of CYP3A cause ≥10-fold increase in area under the curve of sensitive index substrate(s).

++Moderate inhibitor/inducer: increase the area under the curve of sensitive index substrates of a given metabolic pathway ≥2-fold to <5-fold

+Weak inhibitor/inducer: increase the area under the curve of sensitive index substrates of a given metabolic pathway ≥1.25-fold to <2-fold.

ALB indicates ALB1 tyrosine-protein kinase; ALK, anaplastic lymphoma kinase; ANT, anthracycline; ARB, angiotensin receptor blocker; BCL-2, antiapoptotic B-cell lymphoma-2; BCR, breakpoint cluster region; BRM, biological response modulator; BTK, Bruton tyrosine kinase; c-MET, mesenchymal-epithelial transition factor; CCB, calcium channel blocker; CDK, cyclin-dependent protein kinase; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptors; FLT3, FMS-like tyrosine kinase 3; HDAC, histone deacetylase; HER2, human epidermal growth factor receptor 2; HMGCoA, 3-hydroxy-3-methyl-glutaryl-CoA; IDH1/IDH2, isocitrate dehydrogenase 1/2; IMPDH, inosine monophosphate dehydrogenase; I_{Na}, inward sodium current; MEK, mitogen-activated extracellular signal-regulated kinase; Na+/K+ ATPase, sodium-potassium-adenosine triphosphatase; PARP, poly adenosine diphosphate-ribose polymerase; PDE5, phosphodiesterase type 5; PI3Kδ, phosphatidylinositol-4,5-bisphosphate 3-kinase; ROS1, receptor tyrosine kinase; SERM, selective estrogen receptor modulators; SGLT2, sodium-glucose cotransporter-2; TKI, tyrosine kinase inhibitor; Topo-I, topoisomerase-I; Trk, tropomyosin receptor kinase; TS, thymidylate synthase; UGT, uridine 5′-diphospho or UDP-glucuronosyltransferase; and VEGF, vascular endothelial growth factor.

serves as a resource to clinicians for identifying more commonplace DIs by metabolic pathway. Various drug references should be utilized for additional details on DIs with these and other therapeutic classes, and a comprehensive review is recommended. As noted, it may be prudent to check multiple sources when evaluating drug-drug interactions related to cardio-oncology.

Excretion

Medications can be excreted from the body as unchanged entities or removed after the process of metabolization. Often, agents that are metabolized are excreted in feces and pose limited risks for drug-drug interactions.[132] Other agents are dependent on drug efflux transporters to deposit compounds into the renal tubules to complete elimination. The P-gp ABCB1 is one of the most common transporters found in the renal system, and inhibition of this system can lead to increases in medications that are eliminated primarily through the kidney. Vinblastine is one such anticancer agent, and inhibition of ABCB1 through the use of either amiodarone or verapamil can lead to increased concentrations and potential toxicities.[136] Last, medications also may compete for renal elimination. For example, both NSAIDs and select antimicrobials may reduce renal tubular secretion of methotrexate, resulting in elevated methotrexate levels.[3]

Renal elimination also can be affected by changes in glomerular filtration rate or alterations in urinary pH.[136] Chemotherapy agents such as cisplatin can affect the optimal functioning of the kidney and its ability to provide filtration, leading to nephrotoxicity. When these agents are used, clinicians should monitor renal function regularly and adjust any cardiovascular therapy that accumulates and presents risk at a lower glomerular filtration rate such as dofetilide, spironolactone, digoxin, or the various anticoagulant agents.[105,119,123,136] Patient-dependent factors such as age and comorbidities, for example, chronic kidney disease, can alter the process of elimination, and this can be compounded with the use of nephrotoxic agents.

PHARMACOKINETIC CONSIDERATIONS WITH SELECT CARDIOVASCULAR AND CHEMOTHERAPEUTIC AGENTS

Anticoagulants and Antiplatelets

The DOACs are distinct in that each agent is predisposed to DIs according to the route of metabolism (Table 3), either dual CYP3A4 and P-gp (rivaroxaban and apixaban) or P-gp alone (dabigatran and edoxaban), as well as the magnitude of the dependence on these metabolic pathways.[99,130] The significance of the interaction depends on the specific DOAC and the strength of inhibition of the interacting agent on CYP3A4, P-gp, or both isoenzymes. For instance, if apixaban is coadministered with a medication that poses strong dual inhibition of CYP3A4 and P-gp, either a 50% dose reduction or complete avoidance is recommended.[99,130] Extreme caution is warranted because recommendations for avoidance or dose reduction across the 4 DOACs vary considerably within the various types of cancer therapies (eg, VEGF inhibitors, epidermal growth factor receptor inhibitors).[99,130] For example, with idelalisib, a strong CYP3A4 inhibitor and P-gp inhibitor (in vitro), apixaban should be avoided, rivaroxaban necessitates dose reduction or an alternative agent, dabigatran warrants close monitoring, and edoxaban requires no dose adjustment. Unfortunately, unlike warfarin, the efficacy and safety of DOACs cannot be monitored with standard measures of blood clotting. Although assays to measure serum DOAC concentrations exist, they are not routinely available at most sites, and a defined therapeutic range for various indications has not been delineated.[105,123]

Warfarin shares metabolic pathways (major CYP2C9 and minor CYP3A4 substrate) with several cancer therapies that may increase the risk of bleeding or reduce the efficacy of anticoagulation (Table 3).[85] Pharmacokinetic and pharmacodynamic interactions of chemotherapeutic agents and warfarin are described in Tables 1 through 3. Select cancer therapies (eg, fluoropyrimidines, capecitabine, tamoxifen) inhibit warfarin metabolism, and coadministration should be avoided if possible during can-

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Table 4. Management of Clinically Significant Drug-Drug Interaction[1,2,4,99,105,119,122–138]

Enzyme	Effect	Substrate	Management
Cardiovascular agents			
CYP1A2 inhibitors	↑ Substrate concentration	Mexiletine, lidocaine, propafenone, carvedilol, verapamil, triamterene	Monitor for increased AEs; adjust dose or discontinue as warranted.
CYP1A2 inducers	↓ Substrate concentration	Mexiletine, lidocaine, propafenone, carvedilol, verapamil, triamterene	Monitor for no or diminished response; increase dose or avoid as warranted.
CYP2C8 inhibitors	↑ Substrate concentration	Amiodarone, apixaban, torsemide, riociguat	Monitor for increased AEs; adjust dose or discontinue as warranted.
CYP2C8 inducers	↓ Substrate concentration	Amiodarone, apixaban, torsemide, riociguat	Monitor for no or diminished response; increase dose or avoid as warranted.
CYP2C9 inhibitors	↑ Substrate concentration	Warfarin	Select anticancer agents should be avoided or an alternative anticoagulant chosen. If not alternative, preemptive warfarin dose reduction may be warranted, depending on severity of interaction, indication for anticoagulant, and baseline INR. Closely monitor PT/INR and signs/symptoms of bleeding and reduce warfarin dose as indicated.
		Candesartan, irbesartan, losartan*, valsartan	Monitor BP. Dose reduction or alternative anti-HTN may be necessary.
		Fluvastatin, rosuvastatin	Monitor for signs and symptoms of myopathy or rhabdomyolysis. Avoid coadministration with moderate inhibitors (no data with strong inhibitors); change to alternate statin that does not undergo hepatic metabolism (pravastatin) or reduce dose.
		Bosentan	Monitor for increased AEs (headache, hypotension, flushing, reduced hemoglobin).
		Torsemide	Avoid coadministration with moderate inhibitors (no data with strong inhibitors); change to alternate diuretic or reduce dose.
CYP2C9 inducers	↓ Substrate concentration	Warfarin	Select anticancer agents should be avoided and an alternative anticoagulant chosen. If no alternative, preemptive warfarin dose increase may be warranted, depending on severity of interaction, indication for anticoagulant, and baseline INR. Closely monitor PT/INR and lack of efficacy, and increase warfarin dose as indicated.
		Candesartan, irbesartan, losartan, valsartan	Monitor BP and increase anti-HTN dose accordingly.
		Fluvastatin, rosuvastatin	Monitor LDL and increase statin dose accordingly. Add ezetimibe or PCSK9 inhibitor as needed to meet goals.
		Bosentan, torsemide	No dose adjustment needed with mild/moderate inducers (no data with strong inducers).
CYP2C19 inhibitors	↓ Active metabolite concentration	Clopidogrel	Avoid concomitant use. Use prasugrel or ticagrelor if no other contraindications.
	↑ Substrate concentration	Propranolol	Monitor BP and heart rate. Avoid coadministration with severe inhibitors; change to alternative β-blocker that does not undergo hepatic metabolism (eg atenolol) or reduce dose.
CYP2C19 inducers	↑ Active metabolite concentration	Clopidogrel	No dose adjustment needed with mild/moderate/severe inducers.
	↓ Substrate concentration	Propranolol	Monitor BP and increase β-blocker dose accordingly with severe inducers.
CYP2D6 inhibitors	↑ Substrate concentration	Flecainide, propafenone	Use alternative antiarrhythmic agent or monitor for toxicity. including bradycardia (propafenone), widened QRS, and prolonged PR and QT. Consider alternatives to the inhibiting agent (eg, venlafaxine instead of fluoxetine).
		Carvedilol, metoprolol, nebivolol, propranolol	If HFrEF, use bisoprolol. For other indications, use an alternative β-blocker. If no alternative(s), monitor for hypotension or bradycardia.

(*Continued*)

Table 4. Continued

Enzyme	Effect	Substrate	Management
CYP2D6 inducers	NA: no CY2D6 inducers		
CYP3A4 inhibitors	↑ Substrate concentration	Conivaptan, tolvaptan	Avoid ADH antagonist. Alternatively, use fluid restriction or hypertonic saline.
		Lovastatin, simvastatin, atorvastatin	Use pravastatin (preferred), fluvastatin, or rosuvastatin. Add ezetimibe or PCSK9 inhibitors as needed to meet goals. If no alternative(s), then monitor for myopathy.
		Sirolimus, tacrolimus	Avoid if alternative immunosuppressants acceptable. Alternatively, empirically reduce dose and monitor serum concentrations closely.
		Dofetilide, dronedarone, amiodarone	Use alternative antiarrhythmic agent.
		Eplerenone	If HFrEF, use spironolactone. If HTN, use alternative anti-HTN.
		Felodipine, amlodipine	If HTN, use alternative anti-HTN. If angina, use alternative antianginal.
		Sildenafil, tadalafil	If pulmonary HTN, consider agent with alternative MOA. If ED, use alternative agent.
		Ticagrelor	Use clopidogrel or prasugrel if no other contraindications.
		Colchicine	Avoid or use alternative.
		Apixaban, edoxaban (minimal, <4%), rivaroxaban	Apixaban, rivaroxaban: If dual moderate/strong CYP3A4 and P-gp inhibitor, avoid. Combined use of apixaban with idelalisib or ribociclib should be avoided. Combined use of rivaroxaban with ribociclib should be avoided. Apixaban, rivaroxaban, edoxaban: If CYP3A4 inhibitor alone, P-gp inhibitor alone or CYP3A4/P-gp combination with differing strength of inhibition (eg, weak, moderate), potential interaction necessitating caution should be exercised (consider dose adjustment or alternative agent), and monitor for potential toxicity. Note: Not all recommendations are universal (see text for more information).
CYP3A4 inducers	↓ Substrate concentration	Conivaptan, tolvaptan	Avoid ADH antagonist or anticipate reduced efficacy. Alternatively, use fluid restriction or hypertonic saline.
		Lovastatin, simvastatin, atorvastatin	Use pravastatin (preferred), fluvastatin, or rosuvastatin. Add ezetimibe or PCSK9 inhibitors as needed to meet goals
		Sirolimus, tacrolimus	Avoid if alternative immunosuppressants acceptable. Alternatively, empirically increase dose with close monitoring of serum concentrations.
		Dronedarone	Use alternative antiarrhythmic agent.
		Eplerenone	If HFrEF, use spironolactone. If HTN, use alternative anti-HTN.
		Felodipine	If HTN, use alternative anti-HTN. If angina, use alternative antianginal.
		Sildenafil, tadalafil	If pulmonary HTN, consider agent with alternative MOA. If ED, use alternative agent.
		Ticagrelor	Use clopidogrel or prasugrel if no other contraindications.
		Colchicine	Avoid or use alternative.
		Apixaban, edoxaban (minimal, <4%), rivaroxaban	Apixaban, rivaroxaban: If dual moderate/strong CYP3A4 and P-gp inducer, avoid. Combined use of apixaban or rivaroxaban with enzalutamide (CYP3A4 inducer, P-gp inhibitor) should be avoided. Apixaban, rivaroxaban, dabigatran, edoxaban: If CYP3A4 inhibitor alone, P-gp inhibitor alone or CYP3A4/P-gp combination with differing strength of inhibition (eg, weak, moderate), potential interaction necessitating caution should be exercised (consider dose adjustment or alternative agent), and monitor for potential underexposure. Note: Not all recommendations are universal (see text for more information).

(*Continued*)

Table 4. Continued

Enzyme	Effect	Substrate	Management
P-gp inhibitors	↑ Substrate concentration	Apixaban (minimal), dabigatran, edoxaban, rivaroxaban	Apixaban, rivaroxaban: If dual moderate/strong CYP3A4 and P-gp inhibitor, avoid. Combined use of apixaban with idelalisib or ribociclib should be avoided. Combined use of rivaroxaban with ribociclib should be avoided. Apixaban, rivaroxaban, dabigatran, edoxaban: If CYP3A4 inhibitor alone, P-gp inhibitor alone or CYP3A4/P-gp combination with differing strength of inhibition (eg, weak, moderate), potential interaction necessitating caution should be exercised (consider dose adjustment or alternative agent) and monitor for potential underexposure or toxicity. Dabigatran dose adjustment (eg, dose reduction, separate timing) is dependent on indication and patient renal function. Note: Not all recommendations are universal (see text for more information).
		Losartan, labetalol, propranolol, atorvastatin, digoxin	Avoid or monitor therapy closely if unavoidable.
P-gp inducers	↓ Substrate concentration	Apixaban (minimal), dabigatran, edoxaban, rivaroxaban	Apixaban, rivaroxaban: If dual moderate/strong CYP3A4 and P-gp inducer, avoid. Combined use of apixaban and rivaroxaban with enzalutamide (CYP3A4 inducer, P-gp inhibitor) should be avoided. Apixaban, rivaroxaban, dabigatran, edoxaban: If CYP3A4 inhibitor alone, P-gp inhibitor alone, or CYP3A4/P-gp combination with differing strength of inhibition (eg, weak, moderate), potential interaction necessitating caution should be exercised (consider dose adjustment or alternative agent), and monitor for potential underexposure or toxicity. Dabigatran dose adjustment (eg, dose reduction, separate timing) is dependent on indication and patient renal function. Edoxaban: no dose adjustment. Note: Not all recommendations are universal (see text for more information).
		Losartan, labetalol, propranolol, atorvastatin, digoxin	Avoid or monitor therapy closely if unavoidable.
UGT1A1 inhibitors	↑ Substrate concentration	Ezetimibe	Use alternative lipid-lowering agent. If no alternative(s), monitor for decreased response.
UGT1A9 inhibitors	↑ Substrate concentration	Canagliflozin, dapagliflozin	Use alternative SGLT2 inhibitor. If no alternative(s), monitor for reduced efficacy.
		Dabigatran	Use alternative anticoagulant. If no alternative(s), monitor for reduced efficacy.
		Mycophenolate mofetil	Use alternative immunosuppressant. If no alternative(s), monitor for reduced efficacy.
UGT2B7 inhibitors	↑ Substrate concentration	Ezetimibe	Use alternative lipid-lowering agent. If no alternative(s), monitor for reduced efficacy.
		Gemfibrozil	Use alternative lipid-lowering agent. If no alternative(s), monitor for reduced efficacy.
		Losartan	Use alternative ARB. If no alternative(s), monitor for reduced efficacy.
		Lovastatin, simvastatin	Use alternative lipid-lowering agent. If no alternative(s), monitor for reduced efficacy.
UGT1A9 inducers	↓ Substrate concentration	Canagliflozin, dapagliflozin	Use alternative SGLT2 inhibitor. If no alternative(s), monitor for reduced efficacy.
		Dabigatran	Use alternative anticoagulant. If no alternative(s), monitor for reduced efficacy.
		Mycophenolate mofetil	Use alternative immunosuppressant. If no alternative(s), monitor for reduced efficacy.

(*Continued*)

Table 4. Continued

Enzyme	Effect	Substrate	Management
UGT2B7 inducers	↓ Substrate concentration	Ezetimibe	Use alternative lipid-lowering agent. If no alternative(s), monitor for reduced efficacy.
		Gemfibrozil	Use alternative lipid-lowering agent. If no alternative(s), monitor for reduced efficacy.
		Losartan	Use alternative ARB. If no alternative(s), monitor for reduced efficacy.
		Lovastatin, simvastatin	Use alternative lipid-lowering agent. If no alternative(s), monitor for reduced efficacy.
Oncology agents			
CYP1A2 inhibitors	↑ Substrate concentration	Erlotinib	Avoid giving combined CYP3A4 and CYP1A2 inhibitors. If coadministration is unavoidable, reduce erlotinib dose per PI.
		Pomalidomide	Avoid combination. If coadministration is unavoidable, reduce pomalidomide dose per PI.
CYP1A2 inducers	↓ Substrate concentration	Erlotinib	Avoid combination. If smoking continues, increase erlotinib per PI. If smoking is discontinued immediately, reduce erlotinib dose per PI.
		Pomalidomide	Avoid combination or monitor for AEs.
CYP2C8 inhibitors	↑ Substrate concentration	Enzalutamide	Reduce dose by 50%.
		Ifosfamide, dabrafenib, imatinib, ponatinib, paclitaxel, tucatinib	No dose adjustment needed with mild/moderate/strong inhibitors; monitor closely for AEs.
CYP2C8 inducers	↓ Substrate concentration	Enzalutamide	No dose adjustment needed with mild/moderate inducers (no data with strong inducers).
		Ifosfamide, dabrafenib, imatinib, ponatinib, paclitaxel, tucatinib	No dose adjustment needed with mild/moderate inducers (no data with strong inducers).
CYP2C9 inhibitors	↑ Substrate concentration	Bortezomib	No dose adjustment needed with mild/moderate inhibitors (no data with strong inhibitors).
		Tamoxifen	Avoid coadministration with moderate inhibitors or consider a dose reduction (no data with strong inhibitors).
		Imatinib	No dose adjustment needed with mild/moderate inhibitors (no data with strong inhibitors).
	↓ Active metabolite concentration	Cyclophosphamide, ifosfamide	No dose adjustment needed with mild/moderate inhibitors (no data with strong inhibitors).
CYP2C9 inducers	↓ Substrate concentration	Bortezomib, imatinib, romidepsin, tamoxifen, teniposide	No dose adjustment needed with mild/moderate inducers (no data with strong inducers).
	↑ Active metabolite concentration	Cyclophosphamide, ifosfamide	No dose adjustment needed with mild/moderate inducers (no data with strong inducers).
CYP2C19 inhibitors	↑ Substrate concentration	Bortezomib	No dose adjustment needed with mild/moderate inhibitors (no data with strong inhibitors).
		Tamoxifen	Avoid coadministration with moderate inhibitors; consider a dose reduction (no data with strong inhibitors).
		Imatinib	No dose adjustment needed with mild/moderate inhibitors (no data with strong inhibitors).
	↑ Active metabolite concentration	Cyclophosphamide, ifosfamide	No dose adjustment needed with mild/moderate inhibitors (no data with strong inhibitors).
CYP2C19 inducers	↓ Substrate concentration	Bortezomib, imatinib, romidepsin, tamoxifen, teniposide	No dose adjustment needed with mild/moderate/strong inducers.
	↑ Active metabolite concentration	Cyclophosphamide, ifosfamide	No dose adjustment needed with mild/moderate/strong inducers.
CYP2D6 inhibitors	↑ Substrate concentration	Doxorubicin, gefitinib	Avoid combination or monitor for AEs.
	↓ Active metabolite concentration	Tamoxifen	Avoid combination or monitor for reduced efficacy. Consider alternative to the inhibiting agents (eg venlafaxine instead of fluoxetine).
CYP2D6 inducers	NA: no CYP2D6 inducers		

(*Continued*)

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Table 4. Continued

Enzyme	Effect	Substrate	Management
CYP3A4 inhibitors	↑ Substrate concentration	Abemaciclib	Contraindicated or use not recommended (ketoconazole only). If concomitant use needed, dose reduction indicated.
		Acalabrutinib, bosutinib, cobimetinib, crizotinib, everolimus, idelalisib, neratinib, regorafenib, sonidegib, tucatinib, vemurafenib	Contraindicated or use not recommended.
		Axitinib, brigatinib, cabozantinib, ceritinib, dasatinib, duvelisib, encorafenib, fostamatinib, ibrutinib, ivosidenib, lapatinib, larotrectinib, lorlatinib, nilotinib, olaparib, palbociclib, panobinostat, pazopanib, ponatinib, sunitinib, ribociclib, venetoclax	If concomitant use needed, dose adjustment indicated (see PI).
		Dabrafenib, erlotinib, gilteritinib, glasdegib, midostaurin, toremifene	Avoid or monitor for AEs.
CYP3A4 inducers	↓ Substrate concentration	Abiraterone, osimertinib	Contraindicated or use not recommended. If concomitant use needed, dose adjustment indicated (see PI).
		Abemaciclib, apalutamide, axitinib, bosutinib, brigatinib, ceritinib, cobimetinib, crizotinib, dabrafenib, duvelisib, encorafenib, fostamatinib, glasdegib, ibrutinib, idelalisib, ivosidenib, ixazomib, lorlatinib, midostaurin, neratinib, nilotinib, olaparib, palbociclib, panobinostat, pazopanib, ponatinib, regorafenib, ribociclib, sonidegib, sorafenib, tamoxifen, thalidomide, toremifene, tucatinib, vandetanib, venetoclax	Contraindicated or use not recommended.
		Acalabrutinib, cabozantinib, dasatinib, enzalutamide, erlotinib, everolimus, exemestane, gefitinib, imatinib, lapatinib, larotrectinib, sunitinib	If concomitant use needed; dose adjustment indicated (see PI).
		Etoposide, mitotane	Avoid or monitor for reduced efficacy.
		Vemurafenib	Increase dose per PI.
P-gp inhibitors	↑ Substrate concentration	Daunorubicin, doxorubicin, etoposide, irinotecan, lapatinib, paclitaxel, topotecan, vinblastine, vincristine	Avoid or monitor therapy closely if unavoidable.
		Venetoclax	If concomitant use needed, dose adjustment indicated (see PI).
P-gp inducers	↓ Substrate concentration	NA	NA
UGT1A1 inhibitors	↑ Substrate concentration	Belinostat, etoposide, SN-38 (active metabolite of irinotecan)	Avoid combination or monitor for AEs.
UGT1A9 inhibitors	↑ Substrate concentration	Regorafenib, sorafenib, SN-38 (active metabolite of irinotecan)	Avoid combination or monitor for AEs.
UGT2B7 inhibitors	↑ Substrate concentration	NA	NA.
UGT1A4 Inhibitors	↑ Substrate concentration	Pexidartinib	Avoid use with UGT inhibitors. If coadministration is unavoidable, reduce pexidartinib dose according to PI.
UGT1A1 inducers	↓ Substrate concentration	Belinostat, etoposide, SN-38 (active metabolite of irinotecan)	Use caution and evaluate for reduced activity.
UGT1A9 inducers	↓ Substrate concentration	Regorafenib, sorafenib, SN-38 (active metabolite of irinotecan)	Use caution and evaluate for reduced activity.
UGT2B7 inducers	↓ Substrate concentration	NA	NA
UGT1A4 inducers	↓ Substrate concentration	Pexidartinib	Use caution and evaluate for loss of activity.

This table is prepared to provide examples of index substrates and is not intended to be an exhaustive list. Most medications are categorized only under the enzyme which predominantly serves as a substrate or inhibitor/inducer and are not listed multiple times if they serve as such for multiple enzymes.

ADH indicates antidiuretic hormone; AE, adverse event; ARB, angiotensin receptor blocker; BP, blood pressure; CYP, cytochrome P450; ED, erectile dysfunction; HFrEF, heart failure with reduced ejection fraction; HTN, hypertension; LDL, low-density lipoprotein; MOA, mechanism of action; NA, not applicable; P-gp, P-glycoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; PI, package insert; PT/INR, prothrombin time/international normalized ratio; SGLT2, sodium-glucose cotransporter-2; and UGT, uridine 5′-diphospho-glucuronosyltransferase.

*May increase or decrease active metabolites.

cer treatment.[1,6,83,105,110,119,123,128,130] A moderate degree of interaction has been noted with warfarin and other cytotoxic chemotherapy agents such as carboplatin, doxorubicin, vincristine, and TKIs (eg, ibrutinib) through unclear mechanisms in case reports or series.[1,6,83,105,110,119,123,128,130] Therefore, close international normalized ratio monitoring and potential warfarin dose modification may be warranted.

Genetic polymorphisms in drug-metabolizing enzymes or transporters can influence the response to select medications, yet it is unclear whether routine use of genetic testing will improve outcomes. Examples of polymorphisms with a major impact on interindividual variability in drug response and therapeutic outcome include CYP2D6, CYP2C19, and CYP2C9. For example, dose reductions or alternatives agents have been suggested in CYP2C19-poor metabolizers to overcome the risk of adverse effects or lack of efficacy (eg, clopidogrel metabolism to active metabolite). Polymorphisms of CYP2C9 have been linked to NSAID-associated gastrointestinal bleeding.[105,123]

Antiarrhythmics

A notable interaction between an intravenous agent affecting oral therapy is oral digoxin and anthracyclines, both conventional and liposomal, cyclophosphamide, taxanes, and cytarabine (Tables 3 and 4). The extent of digoxin absorption has been noted to be reduced by 50% when coadministered with anthracycline agents.[105,123,126,138] The most likely mechanistic explanation is a combination of upregulation of P-gp and intestinal epithelial toxicity caused by the chemotherapy.[105,123,126,138] The liposomal formulation of anthracyclines may have less induction of P-gp, leading to less impact on absorption, but data are limited.[105,123,126,138] Digoxin elixir, being in solution form, also may be less susceptible to absorption issues. Digoxin levels should be monitored with initiation, dose changes, or discontinuation of the aforementioned chemotherapy agents and if started during the course of these chemotherapy agents.[105,123,126,138]

Several common cardiovascular and cancer therapies are substrates or inhibitors of the CYP2D6 enzyme (Table 3). The β-blockers carvedilol, metoprolol, nebivolol, and propranolol are all important substrates, along with the antiarrhythmics flecainide and propafenone.[105,119,123] Alternative options should be sought before these substrates are combined with strong CYP2D6 inhibitors, but if coadministration should occur, careful monitoring for bradycardia and hypotension with the β-blockers is important (Table 4). Both flecainide and propafenone are inward sodium channel blockers. Flecainide undergoes elimination renally as unchanged drug or by hepatic metabolism through CYP2D6. If it is given concurrently with a CYP2D6 inhibitor, elimination relies more heavily on renal function.[105,119,123] On the other hand, propafenone also has β-blocking properties that become more apparent at higher serum concentrations. It is preferable to select alternative antiarrhythmic agents. If the use of propafenone is unavoidable, an alternative therapy that does not inhibit CYP2D6 should be selected (eg, venlafaxine instead of fluoxetine).[105,119,123,130] If coadministration with a strong CYP2D6 inhibitor is unavoidable, monitoring of these antiarrhythmics should include widened QRS or prolongation of QT or PR intervals and bradycardia, the latter specific to propafenone (Table 4).[127]

Tyrosine Kinase Inhibitors

The introduction of oral TKIs has led to an increased potential for the occurrence of interactions.[111,112] Several TKIs are substrates for CYP3A4 and P-gp, and any inhibition of CYP3A4 and P-gp, as commonly seen with certain cardiovascular medications (eg, amiodarone, verapamil), can lead to increased potential for toxicity (Tables 3 and 4). Likewise, several TKIs can inhibit P-gp, leading to increased bioavailability of cardiovascular substrates (eg, digoxin, anti–factor Xa inhibitors, diltiazem).[131,137] For example, tucatinib can increase this risk of bleeding with rivaroxaban, apixaban, and possibly dabigatran, warranting dose modification, close monitoring, or consideration of an alternative DOAC such as edoxaban that is metabolized only by P-gp (Tables 3 and 4).[105,123,130,131,137]

TKIs are weak bases, and thus, they are poorly absorbed in a nonacidic environment.[131] Although acid suppression therapy, specifically proton pump inhibitors and histamine-2 antagonists, is not classified as a cardiovascular medication, it is often used for gastrointestinal protection when antithrombotic therapy is used in the management of various cardiovascular diseases such as atrial fibrillation, VTE, or post-acute coronary syndrome.[139] If acid suppression therapy is used in conjunction for gastrointestinal bleed prevention for a cardiovascular indication, it is prudent to check the prescribing information for the anticancer agent to determine the most appropriate course of action (eg, avoidance versus separate administration). A unique interaction exists between erlotinib, a CYP1A2 substrate, and tobacco, a key inducer.[119,123] Tobacco smoking plays a large enough role in altering concentrations of erlotinib that recommendations are available to increase the dosing if smoking persists and dose reductions with smoking cessation.

Tamoxifen

Although tamoxifen is metabolized by several CYP enzymes to active metabolites, its most important and potent metabolite, endoxifen, uses CYP2D6 and CYP3A4 pathways. Potent inhibitors of CYP2D6 (eg, amiodarone, labetalol, hydralazine, and several CCBs) reduce the conversion of tamoxifen to endoxifen, potentially reducing the efficacy of the chemotherapeutic agent.[119,123,125,128,133,135] Many important inhibitors of CYP2D6 such as paroxetine, bupropion, fluoxetine, and duloxetine are antidepressants, with varying degrees of inhibition of CYP2D6. Given the overlap of depression with many chronic illnesses, it is important to have a cursory understanding of this important drug-drug interaction (Tables 3 and 4).[119,123,125,128,133,135]

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Interactions With Supportive Care

The cardio-oncology population often requires additional supportive care or palliative therapies (eg, antifungal agents for neutropenic fever, antidepressants), and many of these agents inhibit or induce CYP3A4, CYP2D6, and other CYP enzymes. Thus, a brief discussion about pharmacokinetic DIs with agents not classified as a cardiovascular or cancer therapy is warranted. If a clinically relevant pharmacokinetic interaction exists, selecting either an agent with the least degree of enzyme activity or an alternative therapy is recommended. For example, many patients with cancer have indications for antibiotic or antifungal therapies (eg, febrile neutropenia) that may interact with concomitant cardiovascular and cancer medications. The antibiotic agents clarithromycin and erythromycin are strong CYP3A4 inhibitors, whereas azithromycin has minimal CYP3A4 activity.[128] Similarly, fluconazole has less CYP3A4 inhibition than other -azole antifungal agents.[128,135] Pain therapy, including opioids and nonopioid analgesics, also must be carefully selected. Medications undergoing glucuronidation (eg, dasatinib, imatinib, sunitinib) may interact with acetaminophen and warrant a reduction in the maximum daily acetaminophen dose.[140] Select NSAIDs also may result in interactions (eg, imatinib, dasatinib, and nilotinib may increase ibuprofen concentrations, whereas diclofenac may increase imatinib and dasatinib concentrations). Select cancer therapies may increase opioid concentrations and predispose patients to increased sedation or other effects such as constipation (eg, imatinib and nilotinib and fentanyl, nilotinib and morphine, imatinib and hydrocodone or oxycodone, gefitinib and tramadol).[140] Avoiding antidepressants with CYP3A4, CYP2D6 or other CYP inhibition also may be warranted to avoid clinically relevant DIs with various cardio-oncology therapies. An example of such an agent is tamoxifen, which is a prodrug requiring CYP2D6 metabolism to be pharmacologically active, as denoted in the previous section. The antidepressants with the most inhibition of CYP2D6 include bupropion, fluoxetine, and paroxetine. These are followed by duloxetine and fluvoxamine with moderate inhibition. Citalopram, escitalopram, and sertraline have mild inhibition. Thus, the agents with minimal CYP2D6 that are preferred include mirtazapine, trazodone, and venlafaxine.[135]

PRACTICE CONSIDERATIONS

Table 4 provides recommendations for the management of clinically significant drug-drug interactions with cardiovascular and chemotherapeutic agents. As with Table 3, this information is not comprehensive and multiple resources should be assessed when addressing DIs. Additional practice points are outlined here.

- Several TKIs (eg, dasatinib, ibrutinib, imatinib) depend on acid environments for absorption. Clinicians should evaluate the need for continued acid suppression therapy or select a TKI that is not affected in a basic environment.
  - Inhibition of various renal transporters such as P-gp, organic anion transporter, and BCRP (breast cancer resistance protein) by amiodarone and verapamil can lead to increased levels of renally cleared anticancer agents such as vinblastine, promoting the risk of toxicity. If possible, these cardiovascular agents should be discontinued before therapy is started.
  - Patients on cardiovascular therapies that rely heavily on renal clearance such as digoxin, dofetilide, sotalol, and atenolol should be monitored closely if continued during treatment with nephrotoxic anticancer therapy such as cisplatin. If renal function declines, the dose of the cardiovascular agent should be reduced or the cardiovascular agent discontinued to prevent adverse drug effects.
- Intravenous anthracyclines, both conventional and liposomal, cyclophosphamide, taxanes, cytarabine, and TKI can induce P-gp. Clinicians should be aware of cardiovascular medications that are P-gp substrates and avoid, monitor for reduced efficacy, or assess levels if possible (eg, digoxin).
- Several important chemotherapeutic agents undergo significant DIs. In many cases, a dose reduction or alternative therapy may be warranted. It is critical to review agents for any potential drug-drug interaction.
- Supportive therapies used in the cancer population also can have several important DIs with cardio-oncology agents and need to be considered.
- Pharmacists serve as a uniquely trained resource for addressing both pharmacodynamic and pharmacokinetic interactions, specifically identifying clinically relevant DIs and recommending dose adjustment or alternative therapies to ensure safe and effective medication use.

CONCLUSIONS

The dynamic changes to the therapeutic landscape in cardio-oncology have resulted in the need for increased awareness of pharmacology in relation to clinically significant DIs. The primary goal of a cardio-oncology program is to effectively deliver all lifesaving or disease-modifying cancer therapies while mitigating short- and long-term cardiovascular effects. Understanding the pharmacokinetics/pharmacodynamics of cardiac and cancer therapies is essential to attenuate, minimize, or modify significant DIs. Pharmacists, as part of the multidisciplinary cardio-oncology team, can assist with the mitigation of DI risk, including awareness, use of alternative treatment options or plans, and monitoring. Knowledge of these interactions can lead to the ability to ensure maintenance of lifesaving cancer therapies while avoiding significant toxicities.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Writing Group Disclosures

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Craig J. Beavers	University of Kentucky Healthcare	None	None	None	None	None	None	None
Jo E. Rodgers	University of North Carolina Eshelman School of Pharmacy	NIH/NIA (investigator)*; NIH/NHLBI (steering committee member and investigator)*	None	None	None	None	None	None
Aaron J. Bagnola	The Ohio State University Wexner Medical Center	None	None	None	None	None	None	None
Theresa M. Beckie	University of South Florida College of Nursing/College of Medicine	None	None	None	None	None	None	None
Umberto Campia	Brigham and Women's Hospital–Harvard Medical School	None	None	None	None	None	None	None
Susan Dent	Duke Cancer Institute	Novartis (grant funds for unrelated research project)†	None	None	None	None	Novartis*	None
Katherine E. Di Palo	Montefiore Medical Center	None	None	None	None	None	None	None
Tochi M. Okwuosa	Rush University Medical Center	None	None	None	None	None	None	None
Eugene R. Przespolewski	Roswell Park Comprehensive Cancer Center	None	None	None	None	None	None	None

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*Modest.

†Significant.

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Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Sherry-Ann Brown	Medical College of Wisconsin	None	None	None	None	None	None	None
Richard K. Cheng	University of Washington Medical Center	None	None	None	None	None	None	None
Heather Moore	Duke University	None	None	None	None	None	None	None
David Reeves	Butler University College of Pharmacy and Health Sciences	None	None	None	None	None	None	None

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