Drug-Drug Interactions in Melanoma

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Abstract

Tyrosine kinase inhibitors are indicated for the treatment of a variety of malignancies, but are used commonly in patients with advanced melanoma. Most are also substrates for various efflux transporters, including P-glycoprotein. Due to the frequent use of these agents and the metabolism pathway, serious drug-drug interactions are an increasing risk. This review will focus on both the pharmacokinetic and pharmacodynamic interactions with these agents. Most interactions concern altered bioavailability due to altered stomach pH, metabolism by cytochrome P450 isoenzymes, and prolongation of the QTc interval. This review provides recommendations to guide all advanced practitioners for managing drug-drug interactions, dosing modifications, and drugs to avoid. A complete medication review along with open communication is extremely important within the multidisciplinary health-care team.

Recent advances in the treatment of melanoma have resulted in multiple oral agents, specifically ones targeting BRAF and MEK, as components of the MAPK pathway affect cell growth, differentiation, and survival. Oral agents allow for flexibility and convenience, resulting in improved quality of life. However, these novel targeted drugs have been associated with new challenges. Because of the metabolism associated with these therapies, the potential for serious drug–drug interactions (DDIs) is significant. In contrast, there have been no drug interaction studies conducted with immunotherapies. As always, medication profiles should be reviewed for interactions prior to initiation of therapy.

Dabrafenib, vemurafenib, and cobimetinib are tyrosine kinase inhibitors that are all metabolized by cytochrome P450 (CYP450; Czupryn & Cisneros, 2017). Trametinib is metabolized by the deacetylation and glucuronidation biotransformation pathways, and is therefore less likely to be involved in DDIs (Genentech, 2015, 2018; Novartis, 2018a, 2018b). The most concerning drug-drug interactions with these agents are associated with altered bioavailability due to a change in stomach pH, CYP450 isoenzymes, or prolongation of the QTc interval. These documented DDIs may potentiate adverse events and even lead to reduced therapeutic effects of either drug.

Interactions can be classified as pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions

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arise when absorption, distribution, metabolism, or elimination of the involved drugs is altered, leading to changes in the amount and duration of drug availability at the receptor sites. Pharmacodynamic interactions usually refer to interactions in which active compounds change each other's pharmacologic effects. The effect can be synergistic, additive, or antagonistic (Van Leeuwen, van Gelder, Mathijssen, & Jansman, 2014).

PHARMACOKINETIC INTERACTIONS

Absorption

Gastrointestinal absorption of a drug depends on its inherent characteristics (e.g., bioavailability, solubility) but can also be affected by food and drug–drug interactions. The administration of dabrafenib or cobimetinib with a high-fat meal has been seen to have no effect on the area under the concentration-time curve (AUC) as compared with a fasting state (Ascierto et al., 2016; Hauschild et al., 2012). The potential effect of food on vemurafenib absorption has not been studied, but vemurafenib has been administered without regard to food in clinical trials (Zhang et al., 2017).

A change in stomach pH due to coadministration of an H_2 antagonist proton-pump inhibitor or antacid, as well as the inhibition of P-glycoprotein (P-gp) or other transporters are important factors that can affect the absorption of these agents. According to the package inserts, coadministration of dabrafenib, cobimetinib, or vemurafenib with a proton pump inhibitor for 4 to 5 days may lower therapeutic levels but did not result in a clinically important change in drug exposure (Genentech, 2015; Novartis, 2018a, 2018b). Because dabrafenib, vemurafenib, and cobimetinib are substrates of efflux transporter P-gp, drugs that inhibit P-gp may increase individual drug concentrations. Vemurafenib is also an inhibitor of P-gp, potentially increasing the concentration of coadministered medications (Genentech, 2018). At this time, however, clinical data are nonexistent; more research is needed to fully understand the role of P-gp and oral agents used in the treatment of melanoma.

Metabolism

CYP450 is the most important route of drug metabolism in vivo. CYP enzymes can be inhibited either by competitive binding of two substrates at the same CYP enzyme binding site or uncompetitive inhibition of CYP enzymes by an inhibitor coadministered with a substrate for the same CYP enzymes. Increased or decreased exposure through alteration of CYP activity might cause clinically relevant toxic effects or ineffectiveness of treatment with these agents (Van Leeuwen et al., 2014).

Dabrafenib is metabolized by CYP2C8 and 3A4, so coadministration with strong inducers of these isoenzymes is not recommended (Novartis, 2018a). If coadministration is unavoidable, loss of efficacy may result due to lower dabrafenib concentration levels. Dabrafenib induces CYP3A4, among others, which can result in decreased concentrations and loss of efficacy for hormonal contraceptive substrates and proton pump inhibitors. A patient's international normalized ratio (INR) levels should be monitored more frequently during initiation or discontinuation of dabrafenib due to its inducing activity on CYP2C9.

Vemurafenib and cobimetinib are metabolized by CYP3A4, so inducers and inhibitors of CYP3A4 should be avoided (Genentech, 2015, 2018). If their coadministration is unavoidable, alternative dosing may be recommended, with additional monitoring during therapy and after discontinuation. Vemurafenib also inhibits CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, and 3A4/5. Higher concentrations of concomitant drugs may result, as may adverse reactions (Genentech, 2018). See Table 1 for specific drug-drug interactions.

Encorafenib and binimetinib are also metabolized by CYP3A4. Avoiding strong or moderate inhibitors of CYP3A4 is recommended. If it is unavoidable with short-term use, clinicians can reduce the encorafenib dose to one third of strong CYP3A4 or one half of the dose to concurrent use of moderate CYP3A4 inhibitors. After discontinuation of the offending agent, the patient can be resumed on encorafenib at the initial dose once post 3 to 5 elimination half-lives. Concomitant use of agents with a narrow therapeutic window should be avoided. Due to the recent approval of these agents, drug-drug interaction studies are lacking. Therefore, some agents listed in Table 1 are presumed interactions based on metabolism information (Dummer et al., 2018).

Table 1. Potential Drug–Drug Interactions With BRAF/MEK Inhibitor Combination Therapies

Interaction	Mechanism/ enzyme affected	Recommendations	Potential effects	Drugs to avoid or use with caution
Dabrafenib and trametinib				
Interaction affecting dabrafenib	Metabolized by CYP2C8 CYP3A4	• Avoid strong inducers of CYP2C8 and CYP3A4 monitor for loss of efficacy if unavoidable	Lower dabrafenib levels with potential effects on efficacy	Carbamazepine Clarithromycin Gemfibrozil HIV antivirals Ketoconazole Nefazodone Phenobarbital Phenytoin Pioglitazone Rifampin St. John's wort
		• Avoid strong inhibitors of CYP3A4, CYP2C8, CYP2C9, CYP2C19, or CYP2B6	Higher dabrafenib levels adverse reactions	Atazanavir Ciprofloxacin Clarithromycin Erythromycin Indinavir Itraconazole Ketoconazole Nefazodone
Interactions affecting other drugs	Induces CYP3A4 CYP2B6 CYP2C8 CYP2C9 CYP2C19	• Coadministration of dabrafenib may result in decreased concentrations and loss of efficacy of other drugs	Lower concentrations of concomitant drugs loss of efficacy	Carbamazepine Citalopram Dexamethasone Diazepam Erythromycin HIV antivirals Midazolam Ondansetron Oral contraceptives Pioglitazone Proton pump inhibitors Sirolimus Tacrolimus Warfarin (R or S)
Other potential interactions	Changes in dabrafenib solubility	• Drugs that alter the pH of the upper gastrointestinal tract may decrease systemic exposure of dabrafenib, but the effect on efficacy is unknown	Lower dabrafenib solubility and bioavailability	Antacids Histamine-2 receptor antagonists Proton pump inhibitors

Note. List is not all inclusive. Adapted from Genentech (2015, 2018); Novartis (2018a, 2018b).

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PHARMACODYNAMIC INTERACTIONS

Pharmacodynamic drug–drug interactions can occur when the pharmacologic effect of one drug is changed by another through action on mechanisms associated with the same physiologic process or effect. QTc prolongation is one of the most described pharmacodynamic interactions caused by tyrosine kinase inhibitors. The mechanism or basis is likely the interaction with hERG K+ channels. This interaction results in a change in electronic flow and delayed pulse conduction, leading to QTc prolongation (Van Leeuwen et al., 2014). The potential and degree of QTc prolongation is typically related to the drug's chemical structure and plasma concentration. Further prolongation may be exacerbated by CYP3A4 inhibition by another drug or concomitant use of another agent with QTc prolongation potential. QTc prolongation is known to be concentration-dependent with vemurafenib. Further prolongation has not been documented with vemurafenib when used in

Table 1. Potential Drug–Drug Interactions With BRAF/MEK Inhibitor Combination Therapies (cont.)

Interaction	Mechanism/ enzyme affected	Recommendations	Potential effects	Drugs to avoid or use with caution
Vemurafenib and cobimetinib				
Interactions affecting vemurafenib or cobimetinib	Metabolized by CYP3A4	• Avoid strong or moderate inducers of CYP3A4 and replace with alternative drugs if possible if unavoidable, increase dose of vemurafenib by 240 mg as tolerated • After discontinuation of inducer for 2 wk, resume dose of vemurafenib that was taken prior to the inducer	Lower vemurafenib and cobimetinib levels, loss of efficacy	Carbamazepine Efavirenz Phenobarbital Phenytoin Pioglitazone Rifabutin Rifampin Rifapentine St. John's wort
		• Avoid strong or moderate inhibitors of CYP3A4 and replace with alternative drugs when possible if short-term use is unavoidable, reduce cobimetinib to 20 mg	Higher vemurafenib and cobimetinib levels adverse reactions	Atazanavir Ciprofloxacin Clarithromycin Erythromycin Indinavir Itraconazole Ketoconazole Nefazodone Nelfinavir Saquinavir Suboxone Telithromycin Ritonavir Voriconazole
Interactions affecting other drugs	Vemurafenib inhibits CYP1A2	• Coadministration of vemurafenib with CYP1A2 substrates may increase systemic exposure • Avoid concomitant use of CYP1A2 agents that have a narrow therapeutic window • Monitor closely for toxicities and consider reducing CYP1A2 agents	Higher concentrations of concomitant drugs and adverse events	Apixaban Clozapine Haloperidol Olanzapine Theophylline Tizanidine Zolmitriptan
	Vemurafenib also inhibits CYP2A6 CYP2B6 CYP2C8 CYP2C9 CYP2C19 CYP2D6 CYP3A4/5	• Coadministration of vemurafenib with substrates for these enzymes may increase systemic exposure		Apixaban Duloxetine Fluoxetine Haloperidol Ondansetron Oxycodone Venlafaxine Warfarin
Other potential interactions	Vemurafenib with concurrent checkpoint inhibitors may increase liver enzymes	• The safety and efficacy of vemurafenib in combination with checkpoint inhibitors has not been established	Higher transaminases and bilirubin	Ipilimumab Nivolumab Pembrolizumab
Other potential interactions	Vemurafenib inhibits P-gp transport	• Avoid concurrent use of P-gp substrates with narrow therapeutic indices	Higher concentrations of concomitant drugs	Apixaban Colchicine Digoxin

Note. List is not all inclusive. Adapted from Genentech (2015, 2018); Novartis (2018a, 2018b).

Table 1. Potential Drug–Drug Interactions With BRAF/MEK Inhibitor Combination Therapies (cont.)

Interaction	Mechanism/ enzyme affected	Recommendations	Potential effects	Drugs to avoid or use with caution
Encorafenib and binimetinib				
Interactions affecting encorafenib	Metabolized by CYP3A4	• The effect of coadministration of CYP3A4 inducers have not been studied. Clinical trials suggest lower steady-state encorafenib exposures after the first doses suggesting auto-induction.	Lower encorafenib levels, loss of efficacy	Carbamazepine Phenobarbital Phenytoin Rifabutin Rifampin St. John's wort (presumed interactions)
		• Avoid strong or moderate inhibitors of CYP3A4 and replace with alternative drugs when possible. If short-term use is unavoidable, reduce encorafenib dose to one third of strong CYP3A4 inhibitors or one half of the dose to concurrent use of moderate CYP3A4 inhibitors. After the inhibitor has been discontinued for 3–5 elimination half-lives, resume encorafenib at dose that was taken prior to initiating the CYP3A4 inhibitor	Higher encorafenib levels adverse reactions	Clarithromycin Erythromycin Indinavir Itraconazole Ketoconazole Nefazodone Nelfinavir Saquinavir Simvastatin Suboxone Telithromycin Ritonavir Voriconazole (presumed interactions)
Interactions affecting other drugs	Encorafenib inhibits UGT1A1 CYP1A2 CYP2B6 CYP2C8 CYP2C9 CYP2D6	• Coadministration of encorafenib with substrates may increase systemic exposure. Avoid concomitant use of agents that have a narrow therapeutic window. Monitor closely for toxicities and consider reducing agents.	Higher concentrations of concomitant drugs and adverse events	Diazepam Haloperidol Losartan Theophylline Tizanidine Venlafaxine Verapamil (presumed interactions)
	Encorafenib induces CYP2B6 CYP2C9 CYP3A4	• Coadministration of encorafenib with substrates for these enzymes may decrease systemic exposure	Lower concentrations of concomitant drugs and potential loss of efficacy	
Other potential interactions	Coadministration of encorafenib with hormonal contraceptives	• Avoid hormonal contraceptives alternative non-hormonal contraceptive suggested	Decreased concentrations and loss of hormonal contraceptive efficacy	Oral contraceptives
Other potential interactions	Encorafenib inhibits P-gp transport	• Avoid concurrent use of P-gp substrates with narrow therapeutic indices	Higher concentrations of concomitant drugs	Colchicine Digoxin

Note. List is not all inclusive. Adapted from Genentech (2015, 2018); Novartis (2018a, 2018b).

combination with cobimetinib. According to studies (Bronte et al., 2015), QTc prolongation can occur with single-agent use of dabrafenib and with dabrafenib/trametinib combination (3% of patients vs. 3.8%; Genentech 2015, 2018, Novartis 2018a, 2018b).

Advanced practitioners should be aware of the potential risks of coadministering agents associated with the risk of QTc prolongation. Baseline testing, including assessing electrolyte levels, should be conducted prior to initiating treatment and routinely during therapy. Pharmacists can aid

in reviewing medication profiles to prevent this interaction especially when using 5-HT_3 antagonists, antibiotics, antifungals, and over-the-counter medications.

COMMUNICATION

As with all aspects of patient management, communication regarding potential drug-drug interactions is important among the multidisciplinary health-care team. Pharmacists can assist with medication review and alert other members of the team about the possible need for DDI-related dose modifications or alternative therapies. Additionally, patients should be encouraged to keep a complete medication list (including over-the-counter medications and supplements), and if possible, to attain all refills from one pharmacy to allow for a complete DDI review and the prevention of polypharmacy.

Disclosure

Dr. Norris has no conflicts of interest to disclose.

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