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The Essentials of Drug Interactions in Hematopoietic Stem Cell Transplantation

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Recipients of hematopoietic stem cell transplantation (HCT) receive complex medication regimens that are comprised of cytotoxic agents, immunosuppressants, antimicrobials, supportive drugs, and targeted therapies, in a seemingly endless number of combinations. Virtually none of these medications are without the potential for significant drug-drug interactions as many of them utilize similar metabolism pathways or have overlapping toxicities. Therefore, in order to maximize efficacy and safety of these specialized agents, it is essential to understand of the main drug interactions associated with them. This knowledge becomes even more imperative with the rapid increase in availability and use of targeted therapies in the HCT population.

Pharmacokinetic interactions are the most prevalent category of drug-drug interactions encountered among the medications utilized in HCT, and result in alterations in drug concentration due to changes in the drug's pharmacokinetic profile (e.g., metabolism or absorption). The most common site of these interactions is within the intestine and liver, while the drug undergoes cytochrome P-450 (CYP450)-mediated metabolism, and these tend to be the more clinically relevant and potentially dangerous [1]. Drug interactions due to the CYP3A4 isoenzyme are the most ubiquitous in transplantation pharmacology [1]. The vast majority of drug classes used in HCT either undergo some degree of metabolism, or cause inhibition or induction of CYP3A4 [2]. A comprehensive list of CYP3A4 and other CYP isoenzyme-mediated drug interactions is available in Table 1. These various interactions can cause serious adverse effects if not appropriately managed. For example, fluconazole is a moderate and posaconazole is a strong inhibitor of CYP3A4; therefore, they will both impact the metabolism of the CYP3A4 substrates, tacrolimus, and sirolimus [2,3]. However, the dose adjustments required when these agents are used concomitantly are highly variable, ranging from 25% to 90%, due to differences in the extent of competitive and noncompetitive inhibition that occurs [2,3]. CYP-mediated interactions can also be responsible for toxicity with the use of otherwise relatively benign agents, such as nonabsorbable oral steroids. Budesonide typically has very low systemic absorption, since it undergoes extensive first-pass metabolism, making it an ideal agent to provide local, topical effects within the gastrointestinal tract [4]. However, when voriconazole or posaconazole is coadministered with budesonide, CYP3A4 and other CYP hepatic isoenzymes are significantly inhibited and reduce budesonide metabolism, resulting in markedly increased systemic bioavailability and potential toxicity [4]. It is reasonable to check serum synthetic steroid levels in patients receiving these medications concurrently, particularly prior to tapering budesonide, to avoid manifestations of adrenal insufficiency. The presence of genetic polymorphisms lends an additional complication to consider with CYP interactions. They have been identified in most of the common CYP isoenzymes responsible for drug metabolism, and the frequencies and types encountered are highly variable among different ethnic groups [1,2]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published guidelines on dose adjustments according to CYP polymorphism status for select drugs, such as tacrolimus. It is recommended to check CYP polymorphism status in patients receiving medications for which pharmacogenomic guidance is available. Unfortunately, the level of polymorphism impact on metabolism is known for very few drugs, but it is likely a significant factor for countless others. While this is an area of extensive ongoing research, clinicians should consider checking for CYP polymorphisms in patients who are exhibiting signs of unusual drug metabolism without other identifiable causes.

It is also important to appreciate the significance of pharmacodynamic interactions, which are a result of the physiologic activity or

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Table 1 | Major pharmacokinetic drug interactions among agents used in hematopoietic cell transplantation.

Mechanism	Substrates (Major)	Inhibitors	Inducers
CYP3A4	*Anti-emetics* • Aprepitant, ondansetron	*Anti-emetics* • Aprepitant	*Antibiotics* • Nafcilin
	Azole antifungals • Isavuconazole, itraconazole	*Azole antifungals* • *Moderate*: Fluconazole, isavuconazole • *Strong*: Itraconazole, posaconazole, voriconazole	*Other* • Erythromycin, phenytoin
	Chemotherapeutic agents • Busulfan, cyclophosphamide, etoposide, thiotepa	*Tyrosine kinase inhibitors* • Imatinib, nilotinib	
	Immunosuppressants • Tacrolimus, cyclosporine, sirolimus, steroids		
	Proton pump inhibitors • Lansoprazole, rabeprazole		
	Targeted therapies • Brentuximab, ruxolitinib, ibrutinib		
	Tyrosine kinase inhibitors • Bosutinib, dasatinib, imatinib, nilotinib		
	Other • Amlodipine, benzodiazepines, citalopram, erythromycin, statins		
CYP2C9	*Azole antifungals* • Itraconazole, voriconazole	*Azole antifungals* • *Moderate*: Fluconazole, Isavuconazole, voriconazole	*Anti-emetics* • Aprepitant
	Other • Phenytoin	*Proton pump inhibitors* • Omeprazole	*Chemotherapeutic agents* • Cyclophosphamide
		Tyrosine kinase inhibitors • Nilotinib, sorafenib	*Other* • Phenytoin
CYP2C19	*Azole antifungals* • Isavuconazole, itraconazole, voriconazole	*Azole antifungals* • *Moderate*: Voriconazole • *Strong*: Fluconazole	
	Proton pump inhibitors • Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole		
	Other • Phenytoin, citalopram		
P-glycoprotein	*Anti-emetics* • Ondansetron	*Azole antifungals* • *Moderate*: Fluconazole • *Strong*: Isavuconazole, itraconazole, posaconazole, voriconazole	*Other* • Phenytoin, erythromycin
	Chemotherapeutic agents • Etoposide, methotrexate	*Immunosuppressants* • Cyclosporine	
	Immunosuppressants • Tacrolimus, cyclosporine, sirolimus	*Other* • Mirabegron	
	Targeted therapies • Brentuximab		
	Tyrosine kinase inhibitors • Imatinib, nilotinib, ponatinib		
	Other • Erythromycin		

effects of a drug [1]. This type of drug-drug interaction is exemplified in the significantly increased incidence (10%–15%) of thrombotic microangiopathy (TMA) when tacrolimus and sirolimus are used in combination, which is a relatively rare occurrence (<5%) when each is given as single agent therapy [5]. Some of the most frequently occurring pharmacodynamic interactions in HCT are QTc prolongation and myelosuppression, as these are common adverse effects of many of the medications used in this population. Agents most highly associated with QTc prolongation include fluoroquinolones, azole antifungals, antiemetics (5-HT_3 antagonists, dopamine receptor antagonists, atypical antipsychotics), and tyrosine kinase inhibitors [2]. Myelosuppression frequently occurs after the following medications: immunosuppressants (mycophenolate mofetil), antivirals (ganciclovir/valganciclovir, cidofovir), and targeted therapies (ruxolitinib, ibrutinib) [2,67]. Therefore, it is always important to consider these types of drug interactions when initiating medications. For instance, a patient who reactivates cytomegalovirus while on ruxolitinib and mycophenolate mofetil and has a low-normal neutrophil count should be considered for foscarnet therapy as an alternative to ganciclovir due to the latter's decreased potential to cause myelosuppression.

The information highlighted above only begins to skim the surface of the many drug interactions that exist among the various medications utilized in the HCT population. Awareness of the potential for interactions is absolutely imperative to the safe use of these agents in an already high-risk group, and only becomes more essential as novel agents are employed and medication regimen complexity increases for these patients. This underscores the value of a multidisciplinary team-based approach in the care of HCT patients to optimize outcomes and prevent iatrogenesis.

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