Narrative Review
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Precision Medicine in Oncology Pharmacy Practice

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The objective of this review is to provide an overview of the components, process and resources available to apply precision medicine strategies to drug therapy in cancer medicine, with an emphasis on oncology pharmacy practice. Precision medicine initiatives in oncology take into account individual variability in genes, environment and lifestyle factors. Genomic assays of patient tumors is now the standard of care in oncology and recommendations for targeted drug therapies are often formulated by interprofessional teams. Pharmacogenomics (PGx) is a component of precision medicine based on polymorphisms that impact medication selection and/or dosing. Several oncolytic agents used in the treatment of cancer and supportive care have pharmacogenomic-based dosing recommendations to minimize potential toxicities. Several resources are reviewed here to guide treatment options in oncology as they relate to somatic mutations and PGx. Examples include: OncoKB is a precision oncology knowledge base that offers evidence-based information for somatic mutations. The Clinical Pharmacogenetics Implementation Consortium provides PGx-based guidelines for several oncolytic therapies used to treat cancer and for supportive care. Pharmacists can be integral members of the interprofessional team in many practice settings in precision medicine. Involvement can include membership in molecular tumor boards, PGx dosing services and provide patient education. **Conclusion.** Precision medicine is a rapidly evolving field in oncology that requires an interprofessional approach of drug therapy experts.

Introduction

In 2015, a new Precision Medicine Initiative was launched in the United States to accelerate progress and research toward curing diseases and providing access to personalized information (1). Precision medicine is an emerging approach that takes into account individual variability in genes, environment, and lifestyle factors (1, 2). Precision medicine more accurately predicts which treatment option will work better for a particular disease in a specific group of people. Although used synonymously with personalized medicine, precision medicine is more recently the preferred term as some may misinterpret the word personalized to imply treatments developed uniquely for each individual (versus which approach is best for a specific group of individuals) (2). Oncology has certainly been leading the forefront of precision medicine as many molecular (or somatic) alterations have been identified that drive cancer (1). These somatic mutations are not inherited, are sporadic, and account for the majority of cancers. Many targeted and immunologic therapies have been developed against these mutations and

are successfully being used in the treatment of a variety of cancers.

Pharmacogenomics (PGx) is a component of precision medicine that is defined as the study of how genetic variations may influence an individual's response to drug therapy (3). Pharmacogenetics, on the other hand, often refers to how a single gene may influence a person's response to a drug. Despite differences in definition, pharmacogenomics and pharmacogenetics are commonly used synonymously in general practice. PGx is based on inherited (or germline) polymorphisms in drug metabolizing enzymes or other targets and is currently being used by some oncology practices to improve clinical outcomes, reduce adverse effects, and decrease costs associated with drug therapies (4).

Drug manufacturers have been incorporating pharmacogenomics into the drug development, labeling, and approval processes for several years (5, 6). According to the PharmGKB database at the time of writing, there are 509 annotated drug labels that contain pharmacogenetic information approved by the United States Food and Drug Administration (FDA), European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency, Japan (PMDA), and Health Canada (Sante Canada) (HCSC) (5). Of these, there are 95 annotated drug labels specific to oncology. Biomarker information contained within may include germline polymorphisms, somatic gene mutations, and others. There are multiple PGx dosing guidelines available that have been published by the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Royal Dutch Association for the Advancement of Pharmacy – Pharmacogenetics Working Group), the Canadian Pharmacogenomics Network for Drug Safety and others (7). At the time of writing, each group has produced findings related to oncology practice. For example, there are currently 6 CPIC guidelines available for 10 drugs specifically used in oncology practice (8).

Many other factors affecting drug response should also be taken into account when individualizing drug therapy in a patient with cancer (9). Pharmacokinetic factors such as drug-drug or drug-disease interactions, enzyme inhibition or induction, and environmental factors such as smoking, alcohol, and diet are important considerations. Patient specific factors such as age, sex, renal and hepatic function, performance status, medication adherence, and medication access (financial considerations) should also be assessed. In many clinical pharmacy practices across the country, pharmacists are conducting comprehensive medication therapy reviews, also known as medication therapy management (MTM), in which an individual patient's medications are assessed for interactions, optimal dosing, strategies to minimize adverse drug reactions, minimize costs, and collaborate with other providers to improve treatment outcomes (10). Integration of precision medicine, including pharmacogenomics, with MTM offers a prime opportunity for pharmacists to collaborate with oncologists to further optimize drug selection, dosage, and clinical outcomes. The overall goal is to target the right drug to the right tissue for the right patient while minimizing toxicity.

The focus of this paper is to provide an overview of the components, process, and resources available to apply precision medicine strategies to the most common drug therapies and their pharmacogenomic targets in cancer medicine, with an emphasis on oncology pharmacy practice for both oncolytic and supportive therapies. Specific mutations associated with the tumor itself are briefly reviewed, however just as important are genetic markers associated with the individual patient.

The PubMed biomedical database was searched from 2008 through August 2018

using the Medical Subject Heading (MeSH) keywords: precision medicine, oncology pharmacy practice, pharmacogenomics, and pharmacogenetics (limited to humans, English language, and review articles). OncoKB, PharmGKB, and CPIC guidelines were manually searched for additional references.

Precision Medicine and Oncolytic Drug Therapy Selection

Tumor sequencing of patient tumors is now considered the standard of care in oncology (11). Somatic mutations not only serve as a driver in the development of cancer but also as a therapeutic target for treating cancer. Of the 95 annotated drug labels pertaining specifically to oncology that contain pharmacogenetic information, the FDA requires genetic testing for 49 (5). This field of oncology is rapidly evolving with many new FDA approvals in the pipeline. A new comprehensive precision oncology knowledge base is available (OncoKB) that offers evidence-based information about individual somatic mutations to assist in guiding optimal treatment decisions (11, 12). This knowledge base contains information on FDA approved therapies and agents in clinical trials from a variety of resources and leading experts. Potentially actionable mutations are assigned to one of four levels based on available clinical and laboratory data that support the use of the mutation as a predictive biomarker of drug sensitivity to FDA-approved or investigational agents for a specific indication (11, 12). Table 1 provides a summary of level 1 [biomarker presence recognized by FDA as responsive to FDA-approved drugs for specified indication(s)], level 2 [biomarker presence recognized by standard care as disease responsive to FDA-approved drugs for specified indication(s)], and level R1 [biomarker presence indicates resistance to FDA-approved drugs for specified indication(s)] FDA approved drugs and their associated genes (12). Several other useful genomic knowledge bases are also available that provide information regarding the relevance of genes and their variants (7, 13-15). These databases are updated on a continual basis.

Many precision medicine initiatives are being conducted through the use of interprofessional molecular tumor boards (MTBs) or precision medicine clinics.[4] The goal is often to make clinical recommendations for targeted therapies based on next-generation sequencing (NGS) panels. The interprofessional team may use NGS results to develop an individual patient treatment plan in which a patient may be recommended for standard therapy (an FDA approved targeted therapy), nonstandard FDA-approved targeted therapy (off-label use), or a clinical trial. MTBs often vary in their composition but may include medical oncologists, radiation oncologists, clinical oncology pharmacists, clinical laboratory scientists, molecular genetic scientists, clinical nurses, financial strategists, data managers, coordinators, and others. Some centers are utilizing MTBs as an opportunity to provide interprofessional education for medical oncology fellows, pathology residents, geneticists, pharmacy residents, and students from multiple healthcare professions (4). Several leading cancer centers in the U.S. have published their experiences and outcomes related to their MTBs (16-23).

Pharmacists can have a key role as an interdisciplinary team member in precision medicine. In some cancer centers, clinical pharmacists may be coordinators of MTBs, assist with drug procurement, provide information for and assist with financial assistance programs, manage investigational drug services, participate in data collection and research, and provide comprehensive patient and caregiver education (4). The majority of the oral targeted therapies are

Table 1. Gene Interactions with FDA Approved Oncolytic Agents (11)*

Drug	Disease Indication (s)	Gene (s)
Level 1: Biomarker presence recognized by FDA as responsive to FDA-approved drugs for specified indication (s)		
Ado-trastuzumab emtansine	Breast cancer	ERBB2
Afatinib	Non-small cell lung cancer	EGFR
Alectinib	Non-small cell lung cancer	ALK
Binimetinib + encorafenib	Melanoma	BRAF
Brigatinib	Non-small cell lung cancer	ALK
Ceritinib	Non-small cell lung cancer	ALK
Cetuximab	Colorectal cancer	KRAS
Cobimetinib + vemurafenib	Melanoma	BRAF
Crizotinib	Non-small cell lung cancer	ALK, ROS1
Dabrafenib	Melanoma	BRAF
Dabrafenib + trametinib	Anaplastic thyroid cancer Non-small cell lung cancer Melanoma	BRAF
Dacomitinib	Non-small cell lung cancer	EGFR
Dasatinib	Acute lymphoid leukemia Chronic myelogenous leukemia	ABL1
Enasidenib	Acute myeloid leukemia	IDH2
Erlotinib	Non-small cell lung cancer	EGFR
Everolimus	CNS cancer	TSC1, TSC2
Gefitinib	Non-small cell lung cancer	EGFR
Imatinib	Acute lymphoid leukemia Chronic myelogenous leukemia Gastrointestinal stromal tumor Leukemia Myelodysplasia Myeloproliferative neoplasm Dermatofibrosarcoma protuberans	ABL1, KIT, PDGFRA, PDGFRB
Ivosidenib	Acute myeloid leukemia	IDH1
Lapatinib	Breast cancer	ERBB2
Lapatinib + trastuzumab	Breast cancer	ERBB2
Neratinib	Breast cancer	ERBB2
Nilotinib	Chronic myelogenous leukemia	ABL1
Niraparib	Ovarian cancer	BRCA1, BRCA2
Nivolumab	Colorectal cancer	Microsatellite instability-high
Osimertinib	Non-small cell lung cancer	EGFR
Panitumumab	Colorectal cancer	KRAS
Pembrolizumab	All solid tumors	Microsatellite instability-high
Pertuzumab + trastuzumab	Breast cancer	ERBB2
Regorafenib	Gastrointestinal stromal tumor Colorectal cancer	KIT, KRAS
Rucaparib	Ovarian cancer	BRCA1, BRCA2
Sunitinib	Gastrointestinal stromal tumor	KIT
Trametinib	Melanoma	BRAF

Drug	Disease Indication (s)	Gene (s)
Trastuzumab	Breast cancer, Esophagogastric cancer	ERBB2
Vemurafenib	Non-Langerhans cell histiocytosis/ Erdheim-Chester disease, Melanoma	BRAF
Level 2: Biomarker presence recognized by standard care as disease responsive to FDA-approved drugs for specified indication(s)		
Abemaciclib	Dedifferentiated liposarcoma Well-differentiated liposarcoma	CDK4
Cabozantinib	Renal cell carcinoma Non-small cell lung cancer	MET, RET
Ceritinib	Inflammatory myofibroblastic tumor	ALK
Crizotinib	Inflammatory myofibroblastic tumor Non-small cell lung cancer	ALK, MET
Dasatinib	Gastrointestinal stromal tumor	PDGFRA
Everolimus	Renal cell carcinoma	TSC1, TSC2
Imatinib	Melanoma Gastrointestinal stromal tumor	KIT, PDGFRA
Olaparib	Ovarian cancer	BRCA1, BRCA2
Palbociclib	Dedifferntiated liposarcoma Well-differentiated liposarcoma	CDK4
Sorafenib	Gastrointestinal stromal tumor Thymic tumor	KIT
Sunitinib	Thymic tumor	KIT
Vandetanib	Non-small cell lung cancer	RET
Level R1 – Biomarker presence indicates resistance to FDA-approved drugs for specified indication(s)		
Afatinib	Non-small cell lung cancer	EGFR
Cetuximab	Colorectal cancer	KRAS, NRAS
Erlotinib	Non-small cell lung cancer	EGFR
Gefitinib	Non-small cell lung cancer	EGFR
Imatinib	Gastrointestinal stromal tumor	PDGFRA
Panitumumab	Colorectal cancer	KRAS, NRAS

*Last updated November 5, 2018; ERBB2=Erb-b2 receptor kinase 2; EGFR=Epidermal growth factor receptor; ALK=anaplastic lymphoma kinase; BRAF=B-Raf proto-oncogene serine/threonine-protein kinase; KRAS=Kirsten rat sarcoma viral oncogene homolog; ROS1=ROS proto-oncogene 1; ABL1=Abelson tyrosine-protein kinase 1; IDH2=Isocitrate dehydrogenase 2; TSC1=Tuberous sclerosis 1; TSC2=Tuberous sclerosis 2; KIT=KIT proto-oncogene receptor tyrosine kinase; PDGFRA= Platelet-derived growth factor receptor alpha; PDGFRB=Platelet-derived growth factor receptor beta; IDH1=Isocitrate dehydrogenase 1; BRCA1=Breast cancer type 1 susceptibility gene; BRCA2=Breast cancer type 2 susceptibility gene; CDK4=Cyclin dependent kinase 4; MET=MET proto-oncogene; RET=Ret proto-oncogene; TSC1=TSC complex subunit 1; TSC2=TSC complex subunit 2;NRAS=NRAS proto-oncogene

dispensed from a specialty pharmacy, often separate from the site of the precision medicine clinic or healthcare system. Pharmacists in specialty pharmacies dispense medications that are considered to be complex with high associated cost. They often assist with locating programs for patients who require financial assistance, provide MTM services, and assess for medication adherence (24). In many clinical oncology and specialty pharmacy practice settings, pharmacists provide comprehensive patient and/or caregiver education. For those patients receiving oral oncolytic therapy at home, patient and

caregiver education should not only include information specific to administration of the oral oncolytic and expected side effects, but also how to prevent and manage any side effects in the home setting and safe handling of these medications. Monitoring adherence to oral oncolytic therapy is crucial to the efficacy of these medications (25-27). Pharmacists, nurses, and/or other providers in specialty pharmacies and out-patient cancer clinics perform routine patient phone calls to follow up on medication adherence and to check for medication tolerability and side effects. Pharmacists and other healthcare providers are continually in touch with their patients and provide additional resources as needed.

Once therapy decisions are individualized for a patient, the pharmacist should verify that the chemotherapy regimen is appropriate per protocol (checking for appropriate dose, frequency, and duration of therapy), check for any dose adjustments that may be needed based on renal and/or hepatic function, and review all medications for drug-drug and drug-food interactions. Grapefruit and grapefruit juice commonly interact with oral oncolytic therapies (such as erlotinib, imatinib, lapatinib, palbociclib, and several others) (28). Co-administration of strong CYP3A4 (cytochrome P450 family 3 subfamily A member 4) inhibitors (such as itraconazole, grapefruit/grapefruit juice, and others) can significantly increase the concentration of the oral oncolytic placing the patient at risk of increased toxicity. It is therefore recommended to avoid the concurrent administration of strong CYP3A4 inhibitors with many oral oncolytic agents (28). Appropriate drug-specific supportive care modalities, such as antiemetics, antimicrobials, anti-diarrheals, moisturizers, and others, should also be incorporated into a patient's treatment plan and education. All patients should be prescribed an appropriate antiemetic regimen based on guidelines and individual patient factors (29, 30).

Cancer treatments are very complex, expensive, and require appropriate monitoring and follow up, especially in the home setting for oral oncolytic therapy. Pharmacists are an integral part of the healthcare team in multiple practice settings in precision medicine.

Pharmacogenomic Applications in Oncology

PGx is an evolving field, especially in the realm of clinical pharmacy practice. Many institutions in the United States have established multidisciplinary pharmacogenomic services led by pharmacists (31). Several models of PGx programs have been published both for the in-patient and community setting and more are emerging in the area of oncology practice (32, 33). There are many different enzymes involved in the metabolism of drugs, the most common being the cytochrome P450 (CYP) enzymes. There are approximately 57 CYP genes that encode for their respective enzyme proteins and an extensive number of gene variants which can result in a decrease, loss, or gain of enzyme function (31, 34) Phenotypes based on these gene variants are often organized into simpler groups. For example, CYP2D6 (cytochrome P450 family 2 subfamily D member 6) variants are classified into the following phenotypes: poor, intermediate, extensive, and ultrarapid metabolizers at the time of the CYP2D6 and Codeine CPIC guideline release, though further clarification to five phenotypes has since been made by CPIC and further work is being done to standardize the genotype to phenotype translation at the time of writing (31, 35, 36). Therefore, PGx variants may run the spectrum of causing minimal changes in clinical decision making, to rendering a drug unusable from an efficacy standpoint (e.g., a drug cannot be sufficiently bioactivated for it to be efficacious), to rendering a drug unusable from

a safety standpoint (e.g., a drug produces substantially greater effect such that dangerous side effects or toxicity may emerge) (31). Other drug metabolizing enzymes such as dihydropyrimidine dehydrogenase (DPD), thiopurine methyltransferases, and glucose-6-phosphate dehydrogenase (G6PD) have an important role in PGx. Additionally, other pharmacokinetic and pharmacodynamic effects may be seen via PGx-based changes in receptors and transporters. Pharmacogenomic assessment of metabolizing enzymes can potentially optimize dosing in oncology and minimize drug toxicities. The CPIC guidelines have been designed to help translate genetic laboratory results into actionable prescribing decisions for affected drugs, ultimately optimizing drug therapy (8). Included here is an overview of the CPIC guidelines for drugs used in oncology practice. Although irinotecan is not currently included in CPIC, the PGx of irinotecan will be reviewed briefly. Table 2 provides a summary of pharmacogenomic information for agents used in oncology that are assigned CPIC Level A. Level A indicates that genetic information should be used to change prescribing of the affected drug and recommendations are based from moderate to high level of evidence (8).

5-Fluorouracil, Capecitabine, and Tegafur

5-Fluorouracil (5-FU) and capecitabine are fluoropyrimidine analogues used to treat a variety of solid tumors. Numerous genetic variants of DPYD, the gene that encodes for dihydropyrimidine dehydrogenase (DPD), have been identified (37). DPD is the first and rate-limiting enzyme for fluoropyrimidine catabolism of 5-FU, capecitabine, and tegafur to dihydrofluorouracil (same metabolite for all three fluoropyrimidine analogues). Some of the genetic variants of DPYD do not affect DPD activity, whereas others can significantly decrease enzyme

Table 2. Pharmacogenomic Overview of Oncolytic Agents Assigned CPIC Level A (5, 8)*

Oncolytic Agent	Gene	PGx Level per FDA Labeling†
Oncolytic Agents Used in the Treatment of Cancer		
Capecitabine	DPYD	Actionable PGx
Fluorouracil	DPYD	Actionable PGx
Irinotecan	UGT1A1	Actionable PGx
Mercaptopurine	TPMT, NUDT15	Testing recommended
Tamoxifen	CYP2D6	None
Tegafur‡	DPYD	None
Thioguanine	TPMT, NUDT15	Testing recommended
Agents Used for Supportive Care		
Allopurinol	HLA-B	None
Ondansetron	CYP2D6	Informative PGx
Rasburicase	G6PD	Testing required
Tropisetron§	CYP2D6	None

*Level A indicates that genetic information should be used to change prescribing; †Testing required: testing should be conducted before using this drug; Testing recommended: testing is recommended before using this drug; Actionable PGx: label does not discuss genetic or other testing for gene/protein/chromosomal variants, but does contain information about changes in efficacy, dosage or toxicity due to such variants; Informative PGx: label mentions a gene or protein is involved in the metabolism or pharmacodynamics of the drug, but there is no information to suggest that variation in these genes/proteins leads to different response; ‡Tegafur is assigned CPIC level C: no prescribing actions are recommended; §Tropisetron is not FDA approved in the United States; DPYD=Gene encoding for dihydropyrimidine dehydrogenase; UGT1A1=uridine diphosphate glucuronosyltransferase 1As; TPMT=Thiopurine methyltransferase; NUDT15=Nudix hydrolase 15; CYP2D6=Cytochrome P450 family 2 subfamily D member 6; HLA-B=Human leukocyte antigen B; G6PD=Glucose-6-phosphate dehydrogenase

function placing patients at very high risk of toxicity (nausea/vomiting, neutropenia, diarrhea, stomatitis, mucositis, and/or hand-foot syndrome). Four genetic variants of clinical significance have been identified and include c.1905+1G>A (rs3918290, also known as DPYD*2A, DPYD: IVS14+1G>A); c.1679T>G (rs55886062, DPYD*13, p.I560S); c.2846A>T (rs67376798, p.D949V); and c.1129-5923C>G (rs75017182, HapB3) (37). Approximately 7% of Europeans carry at least one decreased function DPYD variant, the most common variant being HapB3 (4.7%), followed by DPYD*2A (1.6%), and p.D949V (0.7%). In African ancestry, the c.557A>G (rs115232898, p.Y186C) decreased function variant is relatively common with an estimated carrier frequency of 3-5%.

The benefits of genotype-based dosing have been demonstrated in clinical studies, indicating a decreased incidence of 5-FU related toxicities and toxicity-related deaths (37). Dosing recommendations are based on genotype and associated gene activity scores (AS). Carriers with 2 normal function alleles are assigned an AS of 2 and phenotypically are categorized as a normal DPYD metabolizer. Here, normal DPD activity and normal risks for fluoropyrimidine toxicities would be expected and therefore no dosage or therapy adjustments are required. Carriers of one no function or decreased function allele are considered intermediate metabolizers with associated AS of 1 and 1.5 respectively. Significantly reduced DPD activity and severe toxicities can be expected, therefore it is recommended to empirically reduce the initial dose of 5-FU or capecitabine. The recommended dose reductions for intermediate metabolizers are 50% for an AS of 1, and 25% for an AS of 1.5. DPYD poor metabolizers, characterized as carriers with two no function variants, are considered to have complete DPD deficiency and are at very high risk of severe or fatal drug toxicity. 5-FU and capecitabine therapy should be avoided, especially for those with an AS of 0. For those with an AS of 0.5, 5-FU or capecitabine can be considered at a significantly reduced dose if other therapeutic options are not viable. Drug labels for 5-FU and capecitabine currently include warnings and precautions about DPD deficiency (38, 39). The clinical utility for testing for other gene variants that have a role in 5-FU metabolism, such as TYMS and MTHFR, has not been established at this time (8).

Tegafur is a prodrug of 5-FU and is metabolized by the same enzyme pathway as described above for 5-FU and capecitabine. The impact of DPYD variants is limited and dosing adjustments have not been established. Currently there are no PGx recommendations to guide clinical practice for tegafur (37).

Mercaptopurine and Thioguanine

The thiopurines, mercaptopurine (MP) and thioguanine (TG), are commonly used in the treatment of acute lymphoblastic leukemia (ALL) and some autoimmune disorders. Thiopurine methyltransferase (TPMT) is the enzyme responsible for methylation of MP and TG into the respective inactive metabolites, methyl-mercaptopurine and methyl-thioguanine (40). However, in the deficiency or absence of TPMT, the metabolic pathway of MP and TG is shifted to favor the formation of active thioguanine nucleotide (TGN) metabolites which can accumulate and result in an increased potential for severe adverse effects, especially life-threatening myelosuppression. Although TPMT variants are rare overall, ethnic differences in the frequency of low-activity variant alleles have been reported in black, white, and Asian populations (approximately 6, 5, and 3% respectively) (41). Azathioprine is also metabolized through the same pathway as MP and TG, however this drug will not be reviewed here due to its limited utility in oncology.

TPMT status should be tested prior to initiation of therapy with appropriate starting doses of MP or TG adjusted based on genotype (40). Clinical studies have indicated that dose adjustments based on genotype have reduced severe toxicities while maintaining therapeutic effects (40). For patients who are homozygous wild-type or normal TPMT alleles it is expected that there will be lower levels of TGN metabolites and therefore full doses of MP or TG may be initiated. Patients with intermediate activity (heterozygous for TPMT alleles) are not able to tolerate full doses therefore it is suggested to reduce the dose to 30-70% of full starting dose for MP and a reduction of 30-50% of full dose for TG. Patients who are homozygous variant, mutant, low or deficient activity have a 100% risk of developing life-threatening myelosuppression, therefore a 10-fold reduction in dose is recommended along with a decrease in frequency of administration from daily to three times a week. Further monitoring, titration, and dosage adjustments should be considered based on patient response and tolerability. More dosing information is available in the CPIC guidelines (40).

Recent studies have identified variants in the nudix hydrolase 15 (NUDT15) gene that have been strongly associated with thiopurine-related myelosuppression in patients with inflammatory bowel diseases and children with ALL (42). NUDT15 is one of the pathways that converts active thiopurine metabolites (TdGTP and TGTP) to inactive metabolites (TdGMP and TGMP) (41). Patients with defective NUDT15 alleles are at risk of accumulation of these thiopurine active metabolites and therefore thiopurine toxicity (42). Low function alleles are more common in those of Asian ancestry and Hispanic ethnicity (43). Dosing recommendations based on NUDT15 genotypes are currently in process (43).

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator that has a variety of indications in the prevention and treatment of breast cancer (44). Tamoxifen undergoes extensive hepatic metabolism by 2 major pathways, both of which are mediated by CYP2D6 and CYP3A4 enzymes (45). The two major metabolites, endoxifen and 4-hydroxytamoxifen (4HT), have significantly more antiestrogenic activity than the parent compound tamoxifen. Lower endoxifen concentrations and higher risk of breast cancer recurrence have been observed in patients who have low CYP2D6 enzyme activity as a result of CYP2D6 polymorphisms (45, 46). It has been estimated that 17-21% of the Caucasian population may be CYP2D6 poor metabolizers (31). Co-administration of strong CYP2D6 inhibitors (such as fluoxetine or paroxetine) may also significantly reduce endoxifen concentrations. Although other clinical studies have shown conflicting results regarding outcomes and CYP2D6 polymorphisms, the CPIC guidelines indicate that there is uniformly strong evidence that CYP2D6 poor metabolizers (AS = 0) have lower endoxifen concentrations compared to normal metabolizers in the adjuvant setting (45). These patients may be at a higher risk of breast cancer recurrence and worse event-free survival. Due to these increased risks, alternative hormonal therapy for CYP2D6 poor metabolizers is therefore recommended (45). It should be noted that higher doses of tamoxifen (40 mg daily) may not increase endoxifen concentrations equivalent to normal metabolizers and coadministration of weak to strong CYP2D6 inhibitors should be avoided. A moderate recommendation to use alternate hormonal therapy is suggested for those who are intermediate CYP2D6 metabolizers (AS 0.5) and normal metabolizers with the presence

of the *10 allele (AS 1). For those who have no *10 allele present (either intermediate or normal metabolizer, AS 1) the recommendation to consider alternate hormonal therapy is optional at the time of publication (45). No dosage adjustments are needed for CYP2D6 normal metabolizers (AS 1.5 – 2) or ultrarapid metabolizers (AS > 2), however co-administration of moderate to strong CYP2D6 inhibitors should be avoided.

Variation in CYP2C9, CYP3A4, and CYP3A5 genes have been associated with altered 4HT and endoxifen concentrations however clinical outcomes have not been fully elucidated (45). CYP2C19 genotyping has been studied more extensively but conflicting clinical results have not led to any therapeutic recommendations at this time.

Irinotecan

Irinotecan is a key chemotherapeutic agent in the treatment of colon cancer and a variety of other solid tumors. SN-38, the active metabolite of irinotecan, is glucuronidated by uridine diphosphate glucuronosyltransferase (UGT) family, primarily UGT1A1 (47). Genetic variants in the UGT1A1 gene, especially the UGT1A1*28 allele, have been found to be associated with severe toxicities, notably neutropenia and diarrhea. The UGT1A1*28 allele is common in Caucasians (29-45%), Africans (42-51%), and Asians (16%) and has been implicated in Gilbert's syndrome and Crigler-Najjar syndrome. Studies have indicated that patients who are heterozygous and homozygous for UGT1A1*28 had lower maximum tolerated doses of irinotecan compared to those with wild-type alleles (47). Dose reductions for this patient population have not been fully elucidated. The FDA labeling for irinotecan indicates that a reduction in the starting dose of irinotecan by at least one level should be considered for patients who are known to be homozygous for UGT1A1*28 allele (48). CPIC guidelines for irinotecan use in clinical practice have not yet been established.

Rasburicase

Rasburicase is FDA approved for prophylaxis and treatment of hyperuricemia during chemotherapy in adults and children with lymphoma, leukemia, and solid tumors (49, 50). However, rasburicase carries a black box warning indicating that patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency should not receive this drug (49). It is estimated that 5% of the world's population has G6PD deficiency and in certain populations (throughout Asia and Africa) the prevalence may be as high as 30% (50). G6PD is an enzyme important in the pathway associated with nicotinamide adenine dinucleotide phosphate (NADPH) production, a substance that protects erythrocytes from oxidative stress. Erythrocytes that are deficient in G6PD produce lower amounts of NADPH and are therefore at higher risk of oxidative stress and drug-induced hemolytic anemia. Rasburicase is a urate oxidase enzyme that oxidizes uric acid to allantoin and hydrogen peroxide. The administration of rasburicase in patients with known G6PD deficiency has resulted in severe and fatal cases of hemolytic anemia and methemoglobinemia (50). Because of this, rasburicase is contraindicated by the FDA and other agencies in patients with known G6PD deficiency (49, 50). It is recommended that testing for G6PD deficiency should be conducted prior to rasburicase therapy in patients who are at higher risk for G6PD deficiency, such as those with African or Mediterranean ancestry (50). There may be other ancestries, however, that are also at a higher risk of being G6PD deficient. Quantitative enzyme assay should be the preferred screening method due to the variability in G6PD variants that are included in genotype-only tests and high intrasubject variability in females.

Allopurinol

In oncology, allopurinol is often used in the management of hyperuricemia in patients receiving chemotherapy for the treatment of lymphoma, leukemia, and solid tumors (51). The most common indication for allopurinol is for the management of patients with signs and symptoms of primary or secondary gout. In patients with gout, severe cutaneous adverse reactions (SCARs) such as hypersensitivity reactions, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been strongly associated with the human leukocyte antigen (HLA)-B (HLA-B*58:01) variant allele (52). The HLA molecules and genes have an important role in the immune system and HLA-B in particular has been noted to be one of the most polymorphic genes associated with adverse drug reactions. The estimated risk of developing SCAR with allopurinol administration is between 0.1-0.4%, however the mortality risk can be very high (reported up to 25%). The populations at highest risk of HLA-B*58:01 variant and allopurinol-induced SCAR include Taiwan Han-Chinese, Japanese, Korean, Thai, and Europeans (France) (52, 53). Genotyping results are currently reported as HLA-B*58:01 positive (at least one copy of HLA-B*58:01 is present) or negative (no copies of HLA-B*58:01 are detected). For those who are HLA-B*58:01 positive, allopurinol is contraindicated, while patients who are negative may receive standard doses of allopurinol (52, 53). At the time of this writing the FDA has not included HLA-B*58:01 testing in the allopurinol prescribing information (51-53). Drug labeling in Taiwan includes recommendations for HLA-B*58:01 allele testing and Japanese labeling contains precautions (53). It should also be noted that the CPIC guidelines primarily focus on allopurinol therapy for gout (52, 53).

Ondansetron and Tropisetron

The 5-hydroxytryptamine type-3 (5-HT_3) receptor antagonists are used extensively in oncology for the prevention and treatment of chemotherapy and radiotherapy induced nausea and vomiting. Ondansetron is metabolized by the CYP3A4, CYP1A2, and CYP2D6 enzymes to 4 inactive metabolites, whereas tropisetron is metabolized primarily by CYP2D6 to inactive metabolites (54). Other 5-HT_3 receptor antagonists (dolasetron, granisetron, palonosetron, and ramosetron) are metabolized through a variety of other CYP enzymes. The most recent CPIC guideline indicates that patients who are CYP2D6 ultrarapid metabolizers, receiving either ondansetron or tropisetron, may have a higher risk of nausea and vomiting due to increased metabolism of the parent compound (54). If the CYP2D6 genotype is known, it is recommended to consider using an agent that is not predominantly metabolized by CYP2D6, such as granisetron (54). Normal metabolizers may receive standard doses of either ondansetron or tropisetron. There is insufficient evidence for recommendations for CYP2D6 intermediate or poor metabolizers, however these patients could potentially have elevated blood levels of ondansetron placing them at higher risk of QT prolongation (54). Further clinical studies are needed in order to determine this association.

Challenges in Precision Medicine

Based on experiences at other institutions, there have been a multitude of challenges encountered in precision medicine (16, 17, 20, 21, 23, 55). Molecular tumor boards, precision medicine clinics and pharmacogenomic services all require a multidisciplinary approach with appropriate financial, staff, and educational resources. Integration of a good information technology (IT) plat-

form is a critical element to provide genomic information that can be readily shared and interpreted across disciplines. Examples of some limitations and challenges that have frequently been encountered include the following: significant lag time to obtain genomic test results (especially if analysis is conducted off site) and therefore delay in implementation of therapy, timing of genomic testing is often conducted in patients with late stage cancer who have exhausted all other standard therapies, interpretation of test results can be overwhelming and complex, and limited access to targeted therapies and/or clinical trials (16, 17, 20, 21, 23, 55). Genomic test reimbursement and inconsistent payer policies are also significant challenges. Oncolytic drug therapies are very expensive and may be cost prohibitive for many patients and payers. Pharmacogenomic services have not yet been embraced by many institutions and/or oncology pharmacists. Challenges also exist here with respect to costs of tests and lack of reimbursement, turn around time, and interpretation of results. Educational efforts need to continue to improve as many practitioners, even oncologists, have not been adequately trained in molecular biology. There is a compelling need to modernize the genetics content in college curriculums and continuing education efforts to keep practitioners abreast of this ever-evolving field.

Conclusions

Pharmacists are in a prime position to support multi-disciplinary teams in precision medicine by applying PGx to cutting-edge patient centered cancer care. Numerous somatic mutations have been identified that are known to drive cancer. As a result, many therapeutic targets have been developed and many more are in the pipeline. Additionally, PGx is an important and evolving component of precision medicine that can be applied to other medications as well. Dosing strategies based on polymorphisms are important in order to prevent undue toxicities and decrease side effects patients may experience, while still maintaining the medication's clinical efficacy. Numerous opportunities exist in oncology pharmacy practice for precision medicine – molecular tumor boards, MTM, PGx dosing services, patient/caregiver education, continuous professional development, and education for healthcare providers and students. We believe that pharmacists can be a valuable member of the interprofessional team in precision oncology.

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