Opportunities for pharmacogenomics-guided supportive care in cancer

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Variability in response

Early palliative care after diagnosis with advanced cancer improves quality of life (QOL) and may prolong cancer survival [1]. Nonetheless, there is large inter-individual variability in response to drugs used to manage myriad cancer-related symptoms. For example, pain affects more than 75% of cancer patients with advanced disease, but less than one-third achieve pain improvement with conventional strategies within 1 month [2]. Depression affects about one-third of cancer patients and has been linked to poorer prognosis and survival [3]. Despite newer generation antidepressants, about half experience nonresponse to treatment with a first-line antidepressant [3]. Uncontrolled cancer-related symptoms may increase emergency room visits, reduce patient satisfaction, and disrupt cancer treatments.

Pharmacogenomics may improve prescribing

Personalized supportive care medication prescribing using objective tools, such as genomics, may improve drug response [4]. Pharmacogenomics—the impact of genetic variation on drug response—can significantly alter the activity of many supportive care medications, including antidepressants, antiemetics, opioids, and nonsteroidal anti-inflammatory drugs (NSAIDs) [4]. Over 90% of patients carry a pharmacogenetic variant, while nearly one-third carry a variant contributing to supportive oncology medications [4]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) (www.cpicpgx.org) publishes drug-specific, peer-reviewed guidelines on how to best apply pharmacogenomics to guide

therapeutic decision-making, at least one dozen of which are related to supportive care. Integration of pharmacogenomics-guided supportive care prescribing may improve drug efficacy and reduce symptom burden.

Antidepressants

Many selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, and sertraline, are hepatically metabolized and inactivated by cytochrome P450 2C19 (CYP2C19). Due to the presence of loss-of-function alleles, CYP2C19 poor metabolizers (PMs) have increased toxicity risk with such medications, including QT prolongation. Alternatively, those with gain-of-function alleles (rapid [RM] and ultrarapid metabolizers [UMs]) have lower plasma concentrations and increased risk of drug failure. CPIC recommends a 50% dose reduction for CYP2C19 PMs and drug avoidance in UMs [5]. Paroxetine is primarily metabolized by CYP2D6; thus, PMs are at increased risk of adverse effects, particularly gastrointestinal, while UMs are at risk of poor drug response. CPIC recommends avoiding paroxetine in CYP2D6 UMs and PMs [5]. Fluoxetine is metabolized by CYP2D6 and CYP2C19; thus, similar mechanisms can influence drug response. Vortioxetine is primarily metabolized by CYP2D6 and the FDA package insert recommends a maximum dose of 10 mg/day in PMs. Further, polymorphisms in the serotonin transporter gene, SLC6A4, and/or serotonin receptor gene, HTR2A, may result in reduced response to SSRIs [5]. Major depressive disorder is one of the few areas where randomized pharmacogenomics trials have been performed; data suggest that those receiving pharmacogenomics-guided antidepressant selection have improved response compared to those receiving treatment as usual [6].

Antiemetics

Serotonin receptor antagonists (5HT3RAs) are the backbone of prophylaxis and treatment strategies to reduce

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chemotherapy-induced nausea/vomiting. CYP2D6 is the key metabolic enzyme responsible for the inactivation of many 5HT3RAs, especially ondansetron and palonosetron [4]. CYP2D6 UMs quickly degrade ondansetron, resulting in sub-therapeutic drug exposure and poor drug effect. Studies have identified more nausea/vomiting episodes in CYP2D6 UMs receiving ondansetron compared to non-rapid metabolizers [7]. CPIC guidelines recommend alternative antiemetics in CYP2D6 UMs [8]. Granisetron is the sole 5HT3RA that is not metabolized by CYP2D6, and thus may be the most reasonable option in CYP2D6 UMs. One may consider ondansetron dose titrations; however, there is no data to support this.

Opioids

CYP2D6 activates codeine, tramadol, oxycodone, and hydrocodone to stronger opioids: morphine, O-desmethyiltramadol, oxymorphone, and hydromorphone, respectively. Thus, CYP2D6 polymorphisms can significantly alter opioid pharmacology [4]. Codeine-related deaths reported in UMs resulted in a black box warning recommending against its use [9]. Alternatively, PMs may have ineffective analgesia due to impaired activation to morphine. Similar mechanisms are noted with tramadol, as well as oxycodone and hydrocodone but to a lesser degree. CPIC recommends CYP2D6 UMs and PMs avoid opioids metabolized by CYP2D6 (e.g., morphine, hydromorphone) due to increased toxicity or lack of analgesia, respectively [9].

A base-pair substitution in the gene coding the mu-opioid receptor, OPRM1, can result in reduced OPRM1 expression and up to 60–100% more morphine required for analgesia [4]. Analgesia can also be enhanced by the presence of catecholamines, which are metabolized by catechol-O-methyl transferase (COMT). A base-pair substitution in COMT reduces enzyme activity by three to fourfold, increases catecholamine exposure, increases opioid sensitivity, and lowers morphine equivalents required for analgesia, whereas those with higher activity may require at least doubling of the dose [4]. Nonetheless, there is little to no clinical utility of preemptive testing for OPRM1 and/or COMT since best practices suggest dose titration based on analgesic response and tolerability only; however, these results may provide an objective reason as to why higher doses are required in some patients.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are commonly used to manage chronic cancer pain, musculoskeletal pain, and inflammation. Most NSAIDs are hepatically metabolized by CYP2C9, and data suggests that CYP2C9 phenotype alters plasma NSAID concentrations, particularly those with reduced or poor CYP2C9 function resulting in elevated drug concentrations [10]. Because most

NSAID-related side effects, such as gastrointestinal complications, bleeding, and myocardial infarction, are dose-dependent and due to direct COX inhibition, it is reasonable to assume that high drug concentrations increase adverse event risk. Depending on the type of NSAID, CPIC guidelines recommend CYP2C9 PMs to initiate a 25–50% dose reduction or use an alternative not metabolized by CYP2C9, such as aspirin, ketorolac, naproxen, or sulindac. CYP2C9 IMs should also initiate dose reductions or drug avoidance for specific NSAIDs, such as meloxicam, tenoxicam, or piroxicam [10].

Others

There are several drugs vulnerable to pharmacogenomics that are commonly prescribed to cancer populations, such as those undergoing stem cell transplant. Tacrolimus is considered a backbone immunosuppressant for prevention of graft versus host disease in those undergoing an allogeneic transplant. Oral tacrolimus is highly dependent on CYP3A5 metabolism, where IMs and NMs have increased metabolism/inactivation compared to PMs, resulting in lower drug concentration. CPIC recommends CYP3A5 IMs and NMs to initiate oral tacrolimus at 1.5 to 2 times recommended starting dose, followed by therapeutic drug monitoring [11].

Voriconazole is also used post-allogeneic stem cell transplant to prevent development of fungal infections. Its metabolism/inactivation is mediated by CYP2C19. CPIC guidelines recommend alternative antifungals for UMs and RMs, who are at higher risk of drug failure, and PMs who are at higher risk of adverse events [12].

Adopting pharmacogenomics

A concerted effort should be made to evaluate and adopt pharmacogenomics-guided supportive care in cancer. Expanded testing, lower overhead costs, increased reimbursement, and more direct-to-consumer options mean patients will have greater access to pharmacogenomics. Support from medical agencies on how to best integrate pharmacogenomics into medication management and availability of clinical decision support tools is necessary for adoption. The U.S. Food and Drug Administration (FDA) has published tables of pharmacogenomics associations (<https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations>) and incorporates drug-gene information in the package insert. While there is some overlap in drug-gene interactions described by the FDA and CPIC, there is clear divergence in many recommendations which need to be reconciled. Interagency collaboration and greater clarity, awareness, and education on how to effectively adopt pharmacogenomics using evidence-based medicine are crucial in achieving personalized medicine in clinical practice.

Data availability Not applicable

Compliance with ethical standards

Conflicts of interests/competing interests Clinical Advisory Council member for VieCure, Inc.

Code availability Not applicable

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