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Does Pharmacogenomics Account for Variability in Control of Acute Chemotherapy-Induced Nausea and Vomiting with 5-Hydroxytryptamine Type 3 Receptor Antagonists?

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Abstract

Chemotherapy-induced nausea and vomiting is one of the most concerning adverse drug effects from cytotoxic chemotherapy. Despite appropriate use of antiemetic guidelines, 20–30% of patients experience breakthrough nausea and vomiting secondary to chemotherapy. To assess the variability of 5-hydroxytryptamine type 3 receptor antagonist efficacy caused by genetic variation, a review of the available literature was conducted. From the literature, three sources of pharmacogenomic variability were identified: polymorphisms associated with 5-hydroxytryptamine type 3 receptor subunits, drug metabolism via cytochromes P450, and drug transport in the body. Testing for receptor subunit polymorphisms is not applicable to a clinical setting at this time; however, cytochrome P450 2D6 testing is FDA-approved and widely accessible. Cytochrome P450 2D6 ultrarapid metabolizers and poor metabolizers displayed altered antiemetic efficacy when compared with intermediate metabolizers and extensive metabolizers. We postulate that testing for cytochrome P450 2D6 phenotypes may be the most accessible way to provide individualized antiemetic therapy in the future.

Keywords

Pharmacogenomics; Chemotherapy-induced nausea and vomiting; 5-Hydroxytryptamine type 3 receptor antagonists; Cytochrome P450 2D6; Polymorphism; 5-Hydroxytryptamine type 3 receptor subunit

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the most concerning and debilitating adverse drug effects experienced by patients treated with cytotoxic chemotherapy agents [1, 2]. Ineffective control of CINV can contribute to medication noncompliance, patient distress, and decreased quality of life [3]. In order to stratify

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antiemetic treatment, chemotherapy agents have been divided into four groups on the basis of risk of emesis without antiemetic treatment. These groups are high risk (90% or more patients experience emesis), moderate risk (30–90% of patients experience emesis), low risk (10–30% of patients experience emesis), and minimal risk (less than 10% of patients experience emesis) [4–7]. The American Society of Clinical Oncology, the National Comprehensive Cancer Network, the European Society of Medical Oncology, and the Multinational Association of Supportive Care in Cancer guidelines primarily rely on three classes of medications to treat CINV: 5-hydroxytryptamine (5HT; serotonin) type 3 ($5HT_3$) receptor antagonists ($5HT_3$-RAs), neurokinin 1 receptor antagonists, and corticosteroids [4–7].

The emetic pathway is activated through several different mechanisms. A major activator of the chemoreceptor trigger zone is the release of 5HT from enterochromaffin cells in the gut in response to the toxic environment and free radicals created by chemotherapy [1, 8–12]. Since the approval of ondansetron in 1991, $5HT_3$-RAs have played an important role in treating acute CINV in highly and moderately emetogenic chemotherapy regimens [1, 9, 10, 12–14]. Even with appropriate antiemetic regimens, 20–30% of patients still experience breakthrough CINV with chemotherapeutic agents categorized as having high and moderate emetic risk [9, 10, 13, 15]. Variability in emetic control with $5HT_3$-RAs resulted in the examination of the genetic variance in $5HT_3$ receptor subunits, genetic differences in cytochrome P450 (CYP) metabolism of the various $5HT_3$-RAs, and polymorphisms associated with drug transporters [2, 9, 13, 16–19]. This review serves to present the available literature and to discern the impact of pharmacogenomics on $5HT_3$-RA efficacy in patients receiving high- or moderate-emetic-risk chemotherapeutic agents. Table 1 provides a summary of the referenced polymorphisms in drug target and transport genes. Ideally, this review would help guide $5HT_3$-RA selection and improve antiemetic therapy outcomes.

Literature Search Strategy

A multitiered literature search strategy was employed in PubMed. Use of the following medical subject headings (MeSH) terms provided few results: “nausea,” “serotonin,” “receptors, serotonin, 5-ht3,” and “polymorphism, genetic.” A manual search of the review articles during the background research produced 50 original research articles focused on genetic polymorphisms in $5HT_3$ receptors. This method provided more CINV-related results than searching with MeSH terms. To further refine the results, the following terms were used to further exclude articles that involved $5HT_3$, but not CINV: “postoperative nausea and vomiting,” “depression,” “paroxetine,” “irritable bowel syndrome” and “studies conducted in non-human subjects.” Of those 50 articles, 12 were excluded owing to lack of pharmacogenomic information or because they were published before identification of the five subunits of $5HT_3$.

Genetic Polymorphisms Associated with Drug Target: $5HT_3$ Receptors

The $5HT_3$ receptor is a ligand-gated ion channel that is present in the hippocampus, area postrema, and nucleus tractus solitarii [11, 20]. The five subunits that make up the pentamer have been identified as $5HT_{3A}$, $5HT_{3B}$, $5HT_{3C}$, $5HT_{3D}$, and $5HT_{3E}$ [13, 21–23]. The subunits and the genes coding for them have become the target of studies of genetic variation to explain suboptimal control with $5HT_3$-RAs [9, 10, 13, 15, 17, 24].

$5HT_{3A}$

Kaiser et al. [17] sequenced the *HTR3A* gene (codes for the $5HT_{3A}$ subunit) in 233 breast cancer, lung cancer, non-Hodgkin’s lymphoma, Hodgkin’s disease, multiple myeloma, or ovarian cancer patients being treated with highly emetogenic chemotherapies in an attempt

to find a variant associated with CINV and explain the 20–30% variability in $5HT_3$-RA efficacy. These patients received highly emetogenic chemotherapy regimens comprising cyclophosphamide (mean dose 1,554 mg) or cisplatin (mean dose 88 mg), or moderately emetic carboplatin (mean dose 424 mg). Tropisetron or ondansetron was administered before chemotherapy, resulting in 23.7% of patients experiencing vomiting and 35.9% experiencing nausea within the first 24 h [17]. Twenty-one polymorphisms were identified (allelic frequencies ranging from 0.2 to 31.1%); however, no significant correlation to CINV was established [17]. A nonsignificant trend of better CINV control was observed in M257I heterozygotes than in homozygous patients [17]. Kaiser et al. [17] did not support the use of M257I as a pharmacogenetic predictor of $5HT_3$-RA efficacy.

$5HT_{3B}$

The *HTR3B* gene (codes for the $5HT_{3B}$ subunit) must be coexpressed with *HTR3A* to produce a functional $5HT_3$ receptor [21, 22, 25, 26]. The *HTR3B* gene also serves to modify the function of subunit 3A by increasing single channel conductance in 3A/3B heteromeric receptors, making the receptor more responsive to 5HT [16, 25, 26]. Because of its role in the overall function of the $5HT_3$ receptor, Tremblay et al. [16] hypothesized that polymorphisms in the *HTR3B* gene might have an impact on acute CINV and $5HT_3$-RA efficacy. Tremblay et al. sequenced DNA from venous blood samples from the same patients examined by Kaiser et al. The frequencies of the variations highlighted two major polymorphisms: -100_-120delAAG promoter region deletion in the start codon of the *5HT3B* gene (frequency 0.1), linked with a T129S variant (frequency 0.3) in exon 5 [16, 27]. In patients who experienced CINV during both observational periods (0–4 h, 5–24 h), those homozygous for the -100_-120delAAG deletion had a much higher frequency of vomiting than any other patient [16, 17, 27]. After adjustment for Bonferroni correction, the association of -100_-120delAAG deletion and vomiting was deemed not statistically significant [16].

On further examination, multivariate analysis affirmed that the poor CINV control associated with the deletion was not due to the level of chemotherapeutic emetic risk, coadministered medications, or CYP2D6 status [16]. Tremblay et al. suggested that patients who were homozygous for the *HTR3B* gene -100_-120delAAG and were CYP2D6 intermediate metabolizers (IMs) experienced greater CINV incidence than patients with more than one active CYP2D6 gene expressed (extensive metabolizers, EMs, or ultrarapid metabolizers, UMs) [16]. An additive genetic effect was noted in terms of intensity of CINV among wild-type, heterozygous, and homozygous *HTR3B* variant patients [16]. Meineke et al. [27] genotyped 59 healthy patients for the -100_-120delAAG polymorphism to determine the effect of the polymorphism on the *HTR3B* promoter activity. The three-base-pair deletion resulted in a 25–40% increase in promoter activity in vitro, which Meineke et al. [27] concluded would alter the severity of CINV.

Perwitasari et al. [28] conducted a study to compare the frequency of the $5HT_{3B}$ receptor -100_-120delAAG deletion and 18792A>G (rs4938058) and 46698G>A (rs7943062) polymorphisms in 165 Indonesian cancer patients and 188 healthy Caucasians [16, 27]. Significant differences in the AAGAG and AAGGG haplotypes of the *5HT3B* gene between Indonesians and Caucasians were observed ($P < 0.05$) [28]. The haplotype frequency in Indonesians and Caucasians was 19% and 34%, respectively, which may explain the interethnic differences in response to $5HT_3$-RAs [28]. Perwitasari et al. [28] reported that the allele frequencies of the SNPs seen in the Caucasians in the study of Tremblay et al. [16] were closely comparable, implying that disease state has no effect on frequency.

$5HT_{3C}$, $5HT_{3D}$, and $5HT_{3E}$

The discoveries of the *HTR3C*, *HTR3D*, and *HTR3E* genes in 2003 have added to the possible explanations for poor CINV control with $5HT_3$-RAs [29]. Similar to *HTR3B*, *HTR3C*, *HTR3D*, and *HTR3E* also require coexpression with *HTR3A* in order to form functional receptors [30]. Study of the $5HT_{3D}$ subunit has revealed only one SNP nonsignificantly associated with a higher incidence of antiemetic therapy failure in nonresponders [31]. The $5HT_{3E}$ subunit has not yet been studied in CINV.

Fasching et al. [18] assessed $5HT_{3C}$ receptor gene polymorphisms and the incidence of CINV after ondansetron and dexamethasone therapy in 110 German breast cancer patients treated with anthracyclines. The study identified one SNP, K163N (rs6766410), which was associated with an increased incidence of poorly controlled CINV in 50% of C/C homozygous patients ($P = 0.009$) as compared with 22% of A/A (wild type) or A/C patients [18].

A study of $5HT_{3C}$ receptor polymorphisms and failure of $5HT_3$-RAs in 70 Australian cancer patients treated with chemotherapy and dolasetron or tropisetron did not replicate these findings [24]. The variant rs6766410 and two other identified variants were not statistically significant for increased incidence of poorly controlled CINV ($P = 0.266–1.000$) [18, 24]. The study concluded that none of the polymorphisms seen in the $5HT_{3C}$ receptor gene were predictive of $5HT_3$-RA response [24]. Further research, with larger study populations, will be required to validate the findings associated with rs6766410.

The clinical implications of the genetic variability within the individual subunits of the $5HT_3$ receptor remain to be seen. The most variability occurred with the 3B subunit; in which, the -100_-120delAAG deletion has the most potential to explain variation due to the receptor structure. Use of this variability to predict efficacy of CINV control is limited owing to the need for validation across larger and more diverse populations. The 3C, 3D, and 3E subunits have failed to produce any statistically significant variations that could impact clinical decision making.

Genetic Polymorphisms in Drug-Metabolizing Enzymes: The CYPs Affecting $5HT_3$-RA

The CYP family of enzymes is collectively responsible for approximately 75% of drug metabolism in the human body [32]. Of the drugs metabolized by CYPs, approximately 85–95% of them are metabolized by seven specific CYPs: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5 [2, 32]. The $5HT_3$-RAs are not exempt from this, and although they have a conserved mechanism of action, their CYP profiles differ (see Table 2). CYP2D6 is notable as a major metabolic pathway for several of the $5HT_3$-RAs, followed closely by CYP3A. Over 75 allelic variants have been identified for CYP2D6 alone, which creates the potential for a multitude of adverse drug reactions and may alter the efficacy of medications that rely on the enzyme as a major metabolic pathway [33].

Cytochrome P450 2D6

CYP2D6 is well known for its involvement in many drug therapies (e.g., tamoxifen, antipsychotics, tricyclic antidepressants, and selective serotonin reuptake inhibitors). The $5HT_3$-RAs ondansetron, palonosetron, ramosetron, tropisetron, and dolasetron rely on CYP2D6 metabolism in differing degrees. Granisetron is the only $5HT_3$-RA that does not rely on CYP2D6. The identification of a patient's CYP2D6 phenotype may help guide clinician choices in antiemetic therapy. There are four distinct phenotypes of the CYP2D6 enzyme: poor metabolizers (PMs), IMs, EMs, and UMs. Ethnic variability of CYP2D6

phenotypes exists, making polymorphisms harder to predict [33]. The EM phenotype, a "normal patient" who has two functioning alleles, is the commonest across all ethnicities [33, 34]. PMs compose roughly 5–10% of Caucasian patients and are the result of inheritance of two defective genes [34–37]. It is estimated that PMs compose roughly 7% of the Caucasian population and up to 19% of South Africans [33]. The incidence of PMs is virtually undetected in Japanese and Chinese populations (0–2%) and is on average less than 5% in Turkish, Croatian, Asian, African, and Hispanic populations [33]. There is not much evidence to support dose reductions in PM patients, as adverse drug events are typically mild (e.g., headache, fatigue, and constipation).

Attempts have been made to convert a PM to an EM via enzyme induction as a way to decrease the incidence of adverse effects associated with supratherapeutic concentrations; however, CYP2D6 does not react to enzyme induction [35, 38, 39]. Although a PM has low CYP2D6 expression overall, the enzymes that are available function at a high capacity when exposed to supratherapeutic concentrations of CYP2D6-specific HT_3-RAs.

The weakest control of CINV with $5HT_3$-RAs is seen in the UM population [9, 34, 40]. Kaiser et al. [35] reported that four UM patients (1.5%) had a significantly higher mean number of vomiting episodes compared with all the IMs, PMs, and EMs receiving initial doses of cyclophosphamide, cisplatin, or carboplatin, 2.3 ± 2.5 vs 0.2 ± 1.0 (P <0.001) episodes of vomiting, respectively. In addition, UM patients experienced severer nausea than other patients despite use of ondansetron or tropisetron [35]. These patients have at least one active allele and one or two duplication alleles, causing the rapid metabolism of medications and loss of efficacy [35, 37]. The frequency in these patients differs widely among ethnic groups. UMs are present in less than 5% of Caucasian patients (e.g., 4.3% in America, 0.8% in Germany), with the exception of Turkish (8.7%) and Spanish (10%) patients [33, 35]. The frequency differs widely in African and Asian populations: 4.9% in African-Americans, 29% in Ethiopians, 0.9% in Chinese, and 21% in Saudi Arabians [33].

Several options remain for suspected UM patients with poor CINV control. Granisetron is the only $5HT_3$-RA that does not involve CYP2D6 in its metabolism; thus, it might be the most reasonable option in a suspected UM patient [41]. If switching $5HT_3$-RAs does not have an effect on the poorly controlled CINV, the major CINV guidelines support the addition of a neurokinin 1 receptor antagonist [4–7].

It is also important to note the large variability in metabolic activity of IM patients. For example, IM patients with high enzymatic function are very similar to EMs, and IMs with low enzymatic function are hard to discern from PMs. IM patients with true IM behavior would be hard to identify without a CYP2D6 activity probe such as dextromethorphan. Bernard et al. [33] reported only three frequencies of IMs with diminished activity: 1–2% in Caucasian populations, 51% in Asians (excluding Saudi Arabians), and 3–9% in Saudi Arabians. If breakthrough or refractory CINV occurs in these individuals, successful treatment is more difficult as the phenotype is hard to predict without formal testing.

Cytochrome P450 3A4

CYP3A4 is perhaps the most well known drug-metabolizing enzyme in the human body, with approximately 40–60% of drug metabolism being performed by CYP3A4 [34, 36]. Individual variations in enzymatic activity can be traced back to genetics; however, no incontrovertible link has been established as the CYP3A4 gene is highly conserved [34]. Research has been directed at the flanking regions of the CYP3A4 gene, and several mutations have been identified. These mutations may have a potential impact on granisetron, the only $5HT_3$-RA that primarily relies on the CYP3A4 pathway for metabolism. Despite successful in vitro studies, CYP3A4*1B has failed to produce conclusive in vivo evidence

[42]. Research has also identified several other variant alleles, each with no in vivo effects and allele frequencies of 5% or less: CYP3A4*2, CYP3A4*10, CYP3A4*14, CYP3A4*15, and CYP3A4*16 [42].

Hassan and Yusoff [43] conducted a longitudinal prospective observational study among 158 breast cancer patients from Penang, Malaysia, in which they analyzed genetic polymorphisms and their effect on CINV control with granisetron. Each patient was treated with granisetron and dexamethasone, and was followed up within 3–5 days after chemotherapy [43]. The incidence of acute CINV in the Indian population was much lower than the Chinese and Malay populations [43]. This difference was attributed to the absence of CYP3A4*2, CYP3A4*5, CYP3A4*6, and CYP3A4*10 alleles in the Indian population, thus producing higher granisetron concentrations [43]. The CYP3A4*18 mutation that causes decreased enzymatic activity is common among Malay individuals [43]. However, Chinese patients are unlikely to carry mutations (including *4 and *5) that cause decreased activity [43].

The differing frequencies of the CYP2D6 phenotypes and CYP3A4 activity are important to keep in mind as populations increase, health care expands, and genetic testing becomes more accessible. According to projections made after the 2010 US census, the Hispanic population in the USA is expected to triple by 2050 and the Asian population is expected to increase by 4.1%, accounting for 40.6 million US citizens [44]. The variation in CYP2D6 activity currently has the potential for the largest impact in clinical decisions for CINV control. CYP2D6 genotype testing has already been used in different disease states to help individualize patient therapy. Codeine, for example, is commonly known as a prodrug that is dependent on CYP2D6 activity for conversion into morphine [45]. The four phenotypes of CYP2D6 can affect prodrug conversion and thus pain control. For example, UMs are at a significantly increased risk of developing opioid-induced toxicity, whereas PMs may not achieve appropriate therapeutic pain relief [45].

Genetic Variation in Drug Transport: $5HT_3$-RAs

When attempting to explain variability in efficacy of $5HT_3$-RAs, it is important to consider if enough of the administered dose is making it to the target receptor, and if the medication is being removed from the target. The ATP-binding cassette subfamily B member 1 (ABCB1) transporter functions as an efflux pump for a variety of substances, including the $5HT_3$-RAs ondansetron and ramosetron [46, 47]. This is of special significance to antiemetic activity, as ABCB1 is thought to be an active part of the blood–brain barrier. The membrane-associated protein ABCB1 is also known as p-glycoprotein, a multi-drug-resistant protein 1 [46, 47]. The ABCB1 3435C>T variant is correlated with significantly reduced expression of ABCB1, causing increasing concentrations of medications that require ABCB1 for drug efflux [46, 47].

Babaoglu et al. [46] tested the hypothesis that patients with the ABCB1 3435T allele would have superior CINV protection in 216 cancer patients in Turkey and Germany taking granisetron, ondansetron, or tropisetron for moderate to highly emetic chemotherapy. Overall, 40% of patients experienced poor control of CINV in the first 24 h after receiving chemotherapy [46]. Patients who were treated with granisetron and were homozygous for the 3435C>T variation experienced a significantly higher rate of CINV control than patients who were heterozygous or homozygous for the C allele: 92.9% in TT patients versus 47.6% in CT patients ($P = 0.009$) and 56.1% in CC patients ($P = 0.02$) treated with granisetron [46]. The presence of the 3435T variation did not significantly improve CINV control in the ondansetron group, and had no effect in the tropisetron group [46]. Babaoglu et al. [46]

concluded that the ABCB1 variant 3435C>T could explain some pharmacologic variability in efficacy of the $5HT_3$-RAs.

In addition to ABCB1, the $5HT_3$-RAs can also be affected by polymorphisms in the organic cation transporters (OCTs), which are responsible for organic cation uptake in the liver [40]. OCT1 is the commonest form, and has several polymorphisms associated with reduced activity: R61C, C88R, G410S, and M420del [40]. Tzvetkov et al. [40] examined the impact of OCT1 and CYP2D6 polymorphisms on $5HT_3$-RA efficacy in 253 German cancer patients receiving ondansetron or tropisetron for treatment of CINV. Ondansetron concentrations were determined to be independent of OCT1, whereas tropisetron concentrations correlated with OCT1 expression [40]. Genotyping showed that 12% of patients were homozygous for reduced-activity alleles, 38% were heterozygous, and 50% were homozygous for the active alleles [40]. The patients with reduced activity (one or more reduced-activity allele) of OCT1 had increased concentrations of tropisetron, causing greater CINV control than patients homozygous for regular OCT1 activity [40]. Tzvetkov et al. concluded that in addition to CYP2D6 variability, OCT1 polymorphisms could potentially contribute to individual variability in $5HT_3$-RA efficacy. However, the ABCB1 and OCT1 study results do not currently impact clinical decision making owing to their limited findings and the need for further study.

Application of Pharmacogenomics to Personalized CINV Medication Regimens

This review has covered variations in drug target, metabolism, and transport genes, in which pharmacogenomics may impact $5HT_3$-RA efficacy in treating CINV; however, providing individualized patient care based on genetics is not always feasible. Several barriers exist in the translation of pharmacogenomic information to health care providers and clinical practice.

One major issue involves small study populations. For example, the study population never exceeded 300 patients for all the studies noted. These small study populations make detecting an actual polymorphism difficult because of the low (less than 0.1) allele frequencies of a variant, such as the -100_102delAAG variant, which was only expressed in 1.2% of the study population [16]. After a Bonferroni analysis has been performed, the p values of the SNPs were often not statistically significant. Increasing study population sizes will make detecting low-frequency variants easier, and also increase the study's power. Translation to the clinical setting will also be hampered by the need for large study populations, therefore increasing costs and resource demands.

In addition to small populations, studies are typically conducted in isolated patient populations (e.g., breast cancer patients admitted to ward C11 or ward C19 in Penang Hospital) [43]. These isolated groups further contribute to difficulties in detecting actual allele variants. Although studies are easier to conduct with small populations, the small size prevents the results from being extrapolated to a larger population (e.g., Malaysians). Increasing study population sizes seems simple in theory, but not every hospital, clinic, or university has the ability to conduct "in-house" genetic testing. Although, there are several clinical laboratory networks available for pharmacogenomic testing in the USA (e.g., LabCorp, Quest Diagnostics), developing nations often lack these facilities and may only have newly formed pharmacogenomic programs. The root cause of this lack of resources is often a lack of funding, as equipment and personnel needed to collect and interpret pharmacogenomic data can be prohibitively expensive. As a result, increasing study population sizes may be impossible if there is limited access to patient genomic information.

Another major issue with extrapolating the pharmacogenomic data reviewed here is that the only validated pharmacogenomic tests available are for CYP2D6 and CYP3A4. No clinically available test currently exists for $5HT_3$ receptors, ABCB1, or OCT1, all of which contribute to patient variability. Accumulation of sufficient clinical evidence to validate a test's efficacy and predictive powers often takes many years. Additionally, it may take several years before the cost of the test becomes low enough for widespread clinical use. The variants found in the studies were determined by laboratory methods that would be impractical for an individual patient basis.

Testing for CYP2D6 is becoming more convenient in the USA and other developed nations, and is commoner than ever before, but the cost to the patient will always be a barrier. Insurance companies are not always willing to pay for genetic testing, especially for a non-life-threatening condition such as CINV. Bernard et al. [33] reported that in a psychiatric setting, CYP2D6 PM and UM patients cost $4,000 more per year to treat than IM or EM patients. One-time-only CYP2D6 function testing typically costs less than $500, and the results pertain to several other drugs relevant to cancer patients, e.g., tamoxifen, codeine, and antidepressants. However, the cost of a single day in hospital because of drug toxicities quickly exceeds the cost of most commercially available genetic tests. A prime example is early CYP2D6 genotyping of acute lymphoblastic leukemia patients at St. Jude Children's Hospital [45]. These patients will likely use codeine-containing analgesics at some point during their treatment, so identifying PMs and UMs before giving an ineffective or potentially toxic dose is extremely cost-effective [45]. The genotyping results could be directly applied to help guide clinical decisions regarding CINV control with $5HT_3$-RAs.

When compared with the ease and availability of CYP2D6 testing, CYP3A4 erythromycin breath testing (EBT) is a less appealing option. Erythromycin is radiolabeled with ^{14}C, which is N-demethylated in the body and converted to $^{14}CO_2$ and then exhaled [48]. There is a lot of conflicting information about the predictive ability of EBT in many patients; however, Rivory [48] reported that EBT was predictive in the clearance of erythromycin in 16 cancer patients, but further study is required. The pricing and availability of EBT is not readily available, and considering that there are four $5HT_3$-RAs that do not rely on CYP3A4 for primary metabolism, EBT is not an attractive option.

Enhancing our current antiemetic prophylaxis guidelines involves incorporating CYP2D6 phenotypic testing into our laboratory repertoire. Figure 1 depicts a proposed, enhanced treatment algorithm in which each patient who is designated to receive chemotherapy requiring $5HT_3$-RAs (high and moderate emetic risk) is phenotyped before treatment. Another proposed method (not pictured) is to perform genetic testing on every patient receiving a chemotherapy agent with high, moderate, or low emetic risk. This method would not be cost-effective; however, it would provide useful information, as cancer patients often require analgesics and antidepressants which rely on CYP2D6. Another proposed algorithm includes testing individuals who have experienced breakthrough or refractory CINV, in an attempt to isolate UMs. However, the way we adjust our algorithms, CYP2D6 testing is an essential part of providing patients with personalized medical care.

Conclusions

Although many polymorphisms exist that might explain patient variability in $5HT_3$-RA efficacy for acute CINV, the only clinically actionable data points are CYP2D6 and CYP3A4 polymorphisms. We examined several $5HT_3$ receptor subunit polymorphisms; however, most of them could not be directly associated with poor CINV control. More research is needed to establish statistical significance of the 3B -100_-120delAAG variant as a marker of reduced $5HT_3$ receptor function. The recently discovered 3C and 3D subunits

have also been implicated, but the reported variants require validation in larger patient populations and in different ethnicities. Currently, $5HT_3$ receptor subunit E and its implications on CINV have not be elucidated. Aside from the $5HT_3$ receptor functionality and $5HT_3$-RA metabolism, drug transport is the remaining factor. Variations resulting in altered activity of ABCB1 and OCT1 may contribute to the heterogeneity in antiemetic response; however, validation studies and consistent tests for predicted activity are major barriers. Currently in clinical practice, CYP2D6 genetic testing is readily available and may be used to guide future $5HT_3$-RA regimen choices because of its consistent clinical data, relatively low cost, and high patient benefit. As genetic testing becomes more widely accepted and new medications become more patient specific, pharmacogenomics will be an additional tool to help individualize $5HT_3$-RA therapy to prevent and treat CINV.

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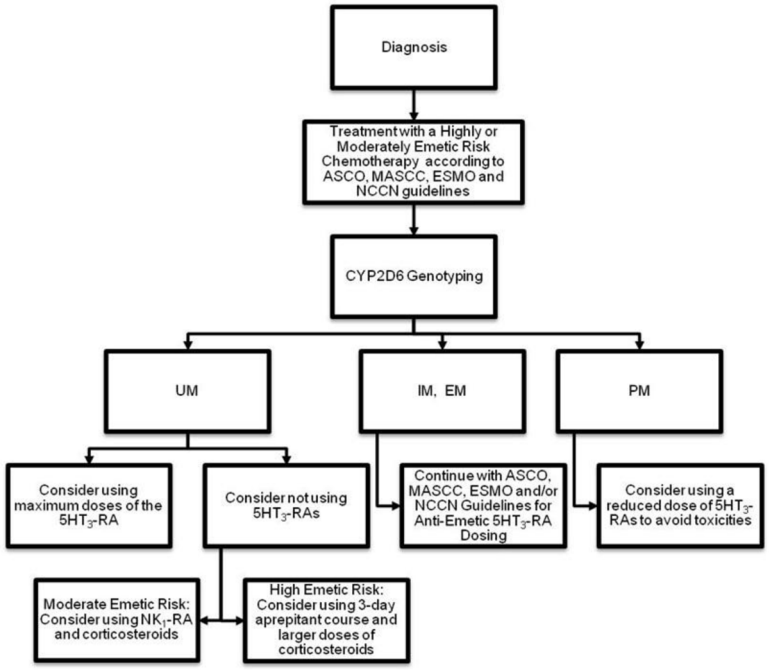

Fig. 1.

An individualized antiemetic treatment algorithm using the cytochrome P450 (*CYP*) 2D6 genotype. An example of an enhanced drug treatment algorithm designed for individualized emetic prophylaxis for patients requiring 5-hydroxytryptamine type 3 receptor antagonists (*5HT$_3$-RAs*). This algorithm suggests performing CYP2D6 genotyping on patients after their diagnosis and the decision to use chemotherapy agents that require 5HT$_3$-RAs. The timing of the genotyping would differ on the basis of institutional ability to do in-house genotyping or the use of a clinical laboratory network. Variations on this algorithm could also include genotyping at diagnosis. *ASCO* American Society of Clinical Oncology, *EM* extensive metabolizer, *ESMO* European Society of Medical Oncology, *IM* intermediate metabolizer, *MASCC* Multinational Association of Supportive Care in Cancer, *NCCN* National Comprehensive Cancer Network, *NK$_1$-RA* neurokinin 1 receptor antagonist, *PM* poor metabolizer, *UM* ultrarapid metabolizer,

Table 1

Referenced polymorphisms

Gene (location)	Sequence	Polymorphism (reference)	Association with poor CINV control	Reference
$5HT_{3A}$ receptor (11q23.1)	NC_000011.9 (113845797..113861035)	A33T	Not associated	Krzywkowski et al. [22]
		M257I	Not associated	Krzywkowski et al. [22], Kaiser et al. [27]
		R344H	Not associated	Krzywkowski et al. [22]
		P391R	Not associated	Krzywkowski et al. [22]
		S253N	Not associated	Krzywkowski et al. [22]
$5HT_{3B}$ receptor (11q23.1)	NC_000011.9 (113775518..113817283)	-100_-120delAAG (rs45460698)	Associated	Tremblay et al. [16], Meineke et al. [27]
		T129S (rs1176744)	Not associated	
		18792A>G (rs4938058)	Not associated	Perwitasari et al. [28]
		46698G>A (rs7943062)	Not associated	Perwitasari et al. [28]
$5HT_{3C}$ receptor (3q27.1)	NC_000003.11 (183770835..183778461)	K163N (rs6766410)	Not associated	Fasching et al. [18], Ward et al. [24]
$5HT_{3D}$ receptor (3q27.1)	NC_000003.11 (183749332..183757157)	G36A (rs6443930)	Not associated	Hammer et al. [31]
ABCB1 (7q21.12)	NC_000007.13 (87133179..87342639, complement)	3435C>T (rs1045642)	Possibly associated	Ishikawa et al. [47]
OCT1 (6q25.3)	NC_000006.11 (160542863..160579750)	R61C	Associated with reduced OCT1 activity	Tzvetkov et al. [40]
		C88R		
		G410S		
		M420del		

5HT3 5-hydroxytryptamine type 3, *ABCB1* ATP-binding cassette subfamily B member 1, *OCT1* organic cation transporter 1

Table 2

Cytochrome P450 (*CYP*) profiles of available $5HT_3$ rector antagonists [2, 43, 49–54]

$5HT_3$-RA	**Major P450(s)**	**Minor P450(s)**	**Notable availability**
Dolasetron (a prodrug, must be converted to reduced dolasetron by carbonyl reductase)	CYP2D6	CYP3A4	Not available in the USA
Granisetron	CYP3A		
Ondansetron	No dominant P450	CYP1A1, CYP1A2, CYP2D6, CYP2E1, CYP3A4	
Palonosetron	CYP2D6	CYP3A, CYP1A2	
Ramosetron	CYP1A2, CYP2D6		Only available in Japan and Southeast Asia
Tropisetron	CYP2D6		Not available in the USA