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ARTICLE

Influence of CYP2D6 metabolizer status on ondansetron efficacy in pediatric patients undergoing hematopoietic stem cell transplantation: A case series

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Abstract

Chemotherapy-induced nausea and vomiting (CINV) is commonly experienced by patients receiving antineoplastic agents prior to hemopoietic stem cell transplant (HSCT). Ondansetron, a 5-HT3 antagonist metabolized by CYP2D6, is an antiemetic prescribed to treat short-term CINV, but some patients still experience uncontrolled nausea and vomiting while taking ondansetron. Adult CYP2D6 ultrarapid metabolizers (UMs) are at higher risk for CINV due to rapid ondansetron clearance, but similar studies have not been performed in pediatric patients. We performed a retrospective chart review of 128 pediatric HSCT recipients who received ondansetron for CINV prevention and had *CYP2D6* genotyping for 20 alleles and duplication detection. The number of emetic episodes for each patient was collected from the start of chemotherapy through 7 days after HSCT. The average age of the cohort was 6.6 years (range: 0.2–16.7) and included three UMs, 72 normal metabolizers, 47 intermediate metabolizers, and six poor metabolizers. Because UMs are the population at risk for inefficacy, we describe the course of treatment for these three patients, as well as the factors influencing emesis: chemotherapy emetogenicity, diagnosis, and duration of ondansetron administration. The cases described support guidelines recommending non-CYP2D6 metabolized antiemetics (e.g., granisetron) when a patient is a known CYP2D6 UM, but pediatric studies with a larger sample of CYP2D6 UMs are needed to validate our findings.

Study Highlights
WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
In adults, ondansetron is not as effective for chemotherapy-induced nausea and vomiting (CINV) in CYP2D6 ultrarapid metabolizers (UMs) compared to non-UMs. Ondansetron is a medication commonly prescribed to pediatric patients, especially for CINV.

WHAT QUESTION DID THIS STUDY ADDRESS?
Our study describes the efficacy of ondansetron for CINV in three pediatric CYP2D6 UMs.
WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
Pediatric CYP2D6 UMs experienced more emesis when taking ondansetron for CINV on days where they did not receive opioids than expected, similar to findings in adults.
HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
Based on these findings, at our institution, any patient undergoing a bone marrow transplant that is a CYP2D6 UM will receive granisetron rather than ondansetron; this practice may be applicable to pediatric patients at other institutions.

INTRODUCTION

Chemotherapy-based conditioning regimens effectively prepare patients for hematopoietic stem cell transplantation (HSCT). Unfortunately, 60–72% of patients receiving chemotherapy experience nausea and vomiting.[1] Chemotherapy-induced nausea and vomiting (CINV) can decrease quality of life, impair ability to perform daily activities, reduce adherence, increase anxiety and depression, increase esophageal tears, malnutrition, and dehydration.[2–5] Additionally, patients have listed nausea and vomiting in the top three most distressing side effects of chemotherapy.[6]

To manage short-term CINV, the American Society of Clinical Oncology (ASCO) recommends 5-HT3 receptor antagonists, such as ondansetron, in its clinical guidelines for adults and children.[7] Although ondansetron has proven efficacy in the reduction of nausea and vomiting, up to 30% of patients who receive the drug still experience CINV.[8,9] This variation in drug effectiveness corresponds to several factors, including variants in the *CYP2D6* gene, which encodes a hepatic enzyme responsible for ondansetron metabolism.[9–12] Studies conducted in adults have demonstrated that CYP2D6 ultrarapid metabolizers (UMs) receiving ondansetron are at an increased risk of experiencing emesis due to rapid ondansetron metabolism.[9,13–15] However, no such studies have been conducted in a pediatric population.

Understanding how pediatric CYP2D6 metabolizer groups respond to ondansetron may allow for personalized antiemetic drug selection and better control of CINV. This could have a direct impact on pediatric HSCT recipients by improving adherence, reducing length of stay, decreasing morbidity, reducing need for total parenteral nutrition, and increasing quality of life. Therefore, the primary objective of this study was to describe the relationship between CYP2D6 metabolizer status and the efficacy of ondansetron in pediatric HSCT recipients. We hypothesized that, similar to adult patients, pediatric CYP2D6 UMs would have poorly controlled emesis compared to other CYP2D6 metabolizers.[16]

METHODS

Retrospective chart review

We performed a retrospective medical chart review after obtaining a list of all patients undergoing bone marrow transplantation at Cincinnati Children's Hospital Medical Center (CCHMC) from August 2013 through July 2019 ($n = 653$; Figure 1). CCHMC's Institutional Review Board provided approval and the database of patient information was de-identified. Individuals were excluded if they were age 18 years or older at the time of HSCT ($n = 91$), if they did not receive a *CYP2D6* genetic test result ($n = 427$), or if they did not receive ondansetron for CINV treatment ($n = 7$). Information regarding type of diagnosis, type of transplant, *CYP2D6* genotype and predicted phenotype, ondansetron administration (dose and frequency), chemotherapy administration (type and dose; Table S1), additional antiemetics administered (Table S2), number of emetic episodes, opioid administration, and CYP2D6 inhibiting drug administration were collected, along with demographics (race, sex, age, weight, and height on day one of ondansetron administration). All patients received an ondansetron dose of 0.15 milligrams per kilogram intravenously every 8 hours, with a maximum dose of 8 milligrams per dose. The dose or choice of antiemetics were not guided by *CYP2D6* testing. Clinician (MD/DO/RN/RD) notes were manually reviewed for mentions of emesis. The institutional standards are documentation of emesis as part of the daily intake and output. Data collection for the number of emetic episodes was limited to the first date of ondansetron administration during the preparative regimen through 7 days after the last dose of chemotherapy, whereas all patients received ondansetron daily. Emetic episodes per non-opioid day were calculated
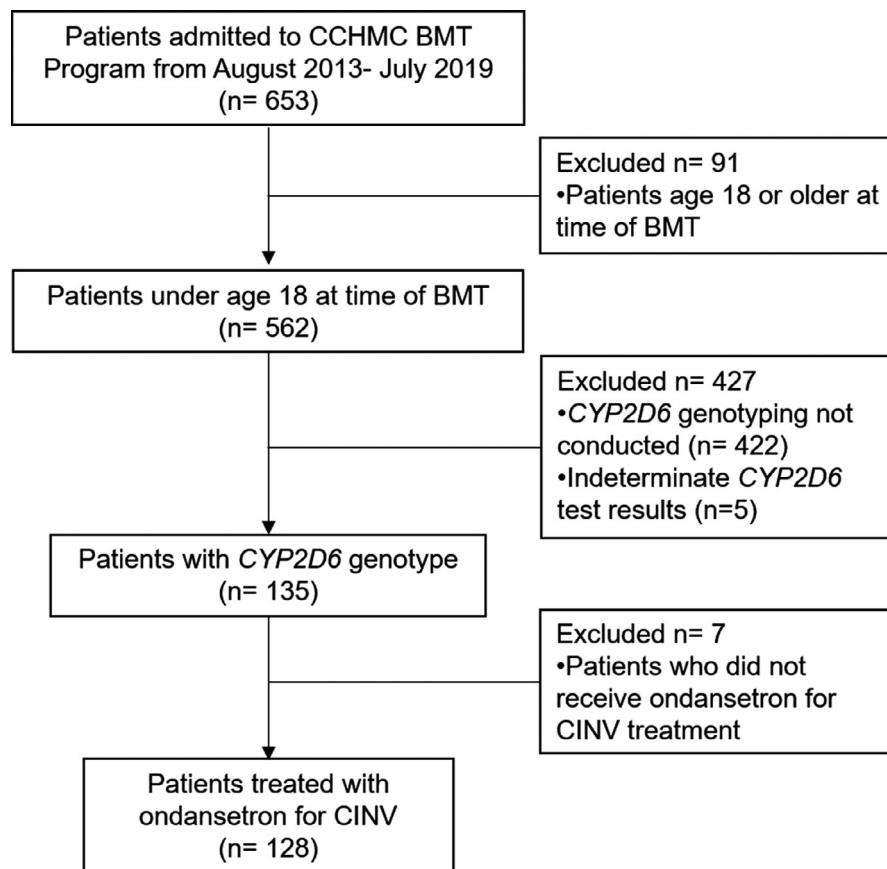
FIGURE 1 CONSORT diagram of patients included in the study. BMT, bone marrow transplantation; CCHMC, Cincinnati Children's Hospital Medical Center; CINV, chemotherapy induced nausea and vomiting; HSCT, hematopoietic stem cell transplantation

as: cumulative number of emetic episodes on non-opioid days/ number of non-opioid days.

Chemotherapy emetogenicity was classified according to the 2017 ASCO Practice Guideline on Antiemetics,[7] which has since been updated.[17] Alemtuzumab was reclassified from moderate to low emetic risk based on clinician experience. Some of the chemotherapies which patients received as a part of their preparative regimen were not encompassed in ASCO's 2017 guidelines, including amifostine, melphalan, and anti-thymocyte globulin (ATG). Therefore, these drugs were categorized according to clinician experience. Amifostine was classified as highly emetogenic, melphalan as moderately emetogenic (now included as minimal in 2020 guideline), and ATG as minimally emetogenic. A list of strong and moderate CYP2D6 inhibiting drugs was obtained from the US Food and Drug Administration website (bupropion, fluoxetine, paroxetine, quinidine, terbinafine, cimetidine, cinacalcet, duloxetine, fluvoxamine, and mirabegron).[18] No patients received a CYP2D6 inhibiting drug during the time of ondansetron administration examined.

CYP2D6 genotyping

CYP2D6 genotyping was performed by CCHMC's Molecular Genetics Laboratory via single gene testing for guidance of opioid selection or as part of a pharmacogenetic panel for voriconazole doing (based on *CYP2C19*) and opioids (*CYP2D6*). This test was included as part of routine care starting in August 2017, and 112 of the 128 patients included were tested after this date. Those tested before may have been tested prior to voriconazole or opioid prescription, after an unexpected reaction to voriconazole or opioids, or part of another research study. Analyses were conducted according to College of American Pathologists and Clinical Laboratory Improvements Amendments standards.[19] The MagNa Pure Compact System (Roche Applied Science, Indianapolis, IN) or Chemagen MSMI (Perkin Elmer, Baesweiler, Germany) was used to isolate genomic DNA. *CYP2D6* genotypes were determined using the TaqMan allelic discrimination system (Life Technology, Forest City, CA) on a low-density microarray using M33388 as a reference sequence. The assay detected 20 *CYP2D6* alleles (*2, *2A, *3, *4, *6, *7, *8, *9, *10, *11, *14, *15, *17, *18, *19, *40, *41, *42, and *44). Full gene deletion (*5 allele) or duplication was detected with a long-range polymerase chain reaction (PCR) assay, as previously described.[20] The *1 genotype was inferred from the absence of the alleles listed above.

Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines were utilized to deduce metabolizer status from *CYP2D6* genotype. CPIC categorizes *CYP2D6* alleles into functional groups with unique activity values

(normal function allele activity value: 1, decreased function allele activity values: 0.25–0.5, no function allele activity value: 0).[21] An individual's total activity score corresponds to their predicted rate of CYP2D6 metabolism and can be calculated from the sum of the activity values for each allele in their diplotype plus the duplicated allele if present.[16] CYP2D6 metabolizer status was determined using the following categories for total activity score: UM (>2.25), normal metabolizer (NM; 1.25–2.25), intermediate metabolizer (IM; 0.25–1), and poor metabolizer (PM; 0).[21] An indeterminate classification was assigned when the laboratory identified a heterozygous diplotype containing a reduced or no function allele and a duplication, but did not distinguish which allele was duplicated ($n = 5$).

Statistical analysis

Descriptive statistics were used to analyze the cohort. Outcome measures included cumulative emetic episodes and emetic episodes per diem (cumulative number of emetic episodes/ total number of days). Emetic episodes on non-opioid days were evaluated separately because nausea and vomiting are known side effects of opioids.[22]

RESULTS

From August 2013 through July 2019, 653 patients were admitted to the Bone Marrow Transplantation Program at CCHMC. Of these patients, 128 met eligibility requirements for our study (Figure 1, Table 1). The median age of patients studied was 5.5 years (interquartile range 2.1–10.2) and three patients were UMs (Table 1). The median number of days analyzed for each patient was 16, with a range of 9–30, and did not differ between metabolizer groups. When considering demographic factors that influence emesis, the median number of emetic episodes experienced by White patients was the same as non-White patients (Table 2). Patients with malignant diagnoses experienced more emetic episodes per day than patients with nonmalignant diagnoses (median 0.72 vs. 0.22, respectively). As expected, the highly emetogenic chemotherapy was associated with a higher median number of emetic episodes per day compared to moderately emetogenic chemotherapy (0.73 vs. 0.31). We also investigated other medications that could be contributing to emesis and identified more episodes of emesis on days where patients received opioids than on non-opioid days (0.5 vs. 0.2). For episodes of emesis per non-opioid day, the same trends of more emesis in malignant diagnoses and those with highly emetogenic chemotherapy regimen were observed, with no differences by sex or race (Table 3).

Figure 2a describes the course the first UM in the cohort, who was a 1-year old boy transplanted for Wiskott-Aldrich Syndrome. His preparatory regimen included antithymocyte globulin, busulfan, and cyclophosphamide (a moderately emetogenic regimen). He started ondansetron the same day as chemotherapy began. Of the 19 days from start of chemotherapy through 1 week after an allogeneic cell infusion, the patient received opioids for 8 days. The patient experienced nine emetic episodes on 11 non-opioid days (0.82 episodes/day) and two emetic episodes on 8 opioid days (0.25 episodes/day), which is

TABLE 1 Study demographics

	PM (n = 6)	IM (n = 47)	NM (n = 72)	UM (n = 3)
Age, median (interquartile range)	7.1 (3.7–14.0)	4.4 (2.0–10.7)	6.3 (2.2–10.2)	5.5 (3.3–6.4)
Sex				
Female, n (%)	3 (50.0%)	19 (40.4%)	32 (44.4%)	1 (33.3%)
Male, n (%)	3 (50.0%)	28 (59.6%)	40 (55.6%)	2 (66.7%)
Race				
White, n (%)	5 (83.3%)	39 (83.0%)	62 (86.1%)	2 (66.7%)
Non-White, n (%)	1 (16.7%)	8 (17.0%)	10 (13.9%)	1 (33.3%)
Diagnosis				
Malignant, n (%)	5 (83.3%)	17 (36.2%)	22 (30.6%)	2 (66.7%)
Nonmalignant, n (%)	1 (16.7%)	30 (63.8%)	50 (69.4%)	1 (33.3%)
Chemotherapy emetogenicity				
High, n (%)	2 (33.3%)	9 (19.1%)	13 (18.1%)	1 (33.3%)
Moderate, n (%)	4 (66.7%)	37 (78.7%)	59 (81.9%)	2 (66.7%)
Low, n (%)	0	1 (2.1%)	0	0

Abbreviations: IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

TABLE 2 Summary of emetic episodes per day in all patients (n = 128)

	Median (IQR)
Sex	
Female (n = 55)	0.35 (0.13–0.67)
Male (n = 73)	0.36 (0.14–0.88)
Race	
White (n = 108)	0.36 (0.14–0.76)
Non-White (n = 20)	0.36 (0.13–0.72)
Diagnosis	
Malignant (n = 46)	0.72 (0.36–0.98)
Nonmalignant (n = 82)	0.22 (0.11–0.57)
Chemotherapy emetogenicity	
High (n = 25)	0.73 (0.36–1.07)
Moderate (n = 102)	0.31 (0.13–0.68)
Low (n = 1)	0.06
Opioids administered on that day	
Yes (n = 762 days)	0.5 (0.11–1.0)
No (n = 1328 days)	0.2 (0–0.59)

Abbreviation: IQR, interquartile range.

TABLE 3 Summary of emetic episodes per non-opioid day in all patients (n = 128)

	Median (IQR)
Sex	
Female (n = 55)	0.18 (0–0.45)
Male (n = 73)	0.21 (0.07–0.69)
Race	
White (n = 108)	0.20 (0–0.66)
Non-White (n = 20)	0.16 (0.06–0.5)
Diagnosis	
Malignant (n = 46)	0.5 (0.09–1.0)
Nonmalignant (n = 82)	0.15 (0–0.40)
Chemotherapy emetogenicity	
High (n = 25)	0.5 (0.19–1.0)
Moderate (n = 102)	0.17 (0–0.5)
Low (n = 1)	0

Abbreviation: IQR, interquartile range.

more emetic episodes per non-opioid day than the upper quartile for patients with moderately emetogenic regimens (0.17 episodes per non-opioid day and 0.44 episodes per opioid day; Table 3, Figure 3). One additional antiemetic (diphenhydramine) was administered during this time period.

Figure 2b shows another UM in the cohort, a 5-year-old girl with neuroblastoma whose preparatory regimen included cyclophosphamide and thiotepa (a highly emetogenic regimen) prior to an autologous transplant. Of the 15 days from start of chemotherapy through 1 week after cell infusion, the patient received opioids for 7 days. The patient experienced 15 emetic episodes on 8 non-opioid days (1.88 episodes/day) and seven emetic episodes on 7 opioid days (1 per day). This is the highest value observed for any patient on highly emetogenic regimens (median 0.50 episodes per non-opioid day and 0.88 episodes per opioid day; Table 3, Figure 3). Three antiemetics besides ondansetron were administered during this time period (diphenhydramine, promethazine, and scopolamine).

The third UM was a 7-year-old boy with Down Syndrome and relapsed acute lymphoblastic leukemia who received a preparatory regimen of cyclophosphamide and fludarabine (a moderately emetogenic regimen) prior to a chimeric antigen receptor T cell infusion. During the 14 days from start of chemotherapy through 1 week after cell infusion, the patient did not receive opioids. The patient experienced two emetic episodes (0.14 per day), which is similar to the median of 0.17 episodes per non-opioid day after a moderately emetogenic regimen (Table 3). He received one additional antiemetic (diphenhydramine) beginning on the day of cell infusion.

DISCUSSION

Our study is the first to our knowledge to describe a potential lack of efficacy of ondansetron in pediatric CYP2D6 UMs. Two of the three CYP2D6 UMs experienced more emetic episodes on non-opioid days than the population median for similarly emetogenic regimens. This is consistent with findings of studies conducted in adult populations[9,13–15] and was enough to prompt our HSCT clinical pharmacy specialist to recommend granisetron rather than ondansetron in known CYP2D6 UMs, where CYP2C19 and CYP2D6 testing is part of routine care.

CPIC created 5-HT3 antagonist selection guidelines for UMs based on findings of the aforementioned studies conducted in adults, recommending a 5-HT3 antagonist metabolized independently of CYP2D6, such as granisetron.[16] Although the universal administration of granisetron would bypass issues associated with CYP2D6 polymorphism, granisetron can be up to ten times more costly than ondansetron.[23] Therefore, CPIC guidelines aim to maximize the therapeutic benefit for adult UMs while avoiding a drastic increase in healthcare costs.[24]

Although 5-HT3 antagonists, such as ondansetron, are encompassed by ASCO's recommendations for CINV treatment in children, the CPIC 5-HT3 antagonist selection guidelines does not give specific advice for

FIGURE 2 Individual descriptions of the course of treatment of three CYP2D6 ultrarapid metabolizers. Orange triangle: date on which the patient started chemotherapy, started ondansetron, received cell infusion, experienced an emetic episode, or received an antiemetic besides ondansetron; purple bar: dates on which opioids were administered; green bar: total days of ondansetron administration; blue: total days without opioid administration during period of ondansetron administration
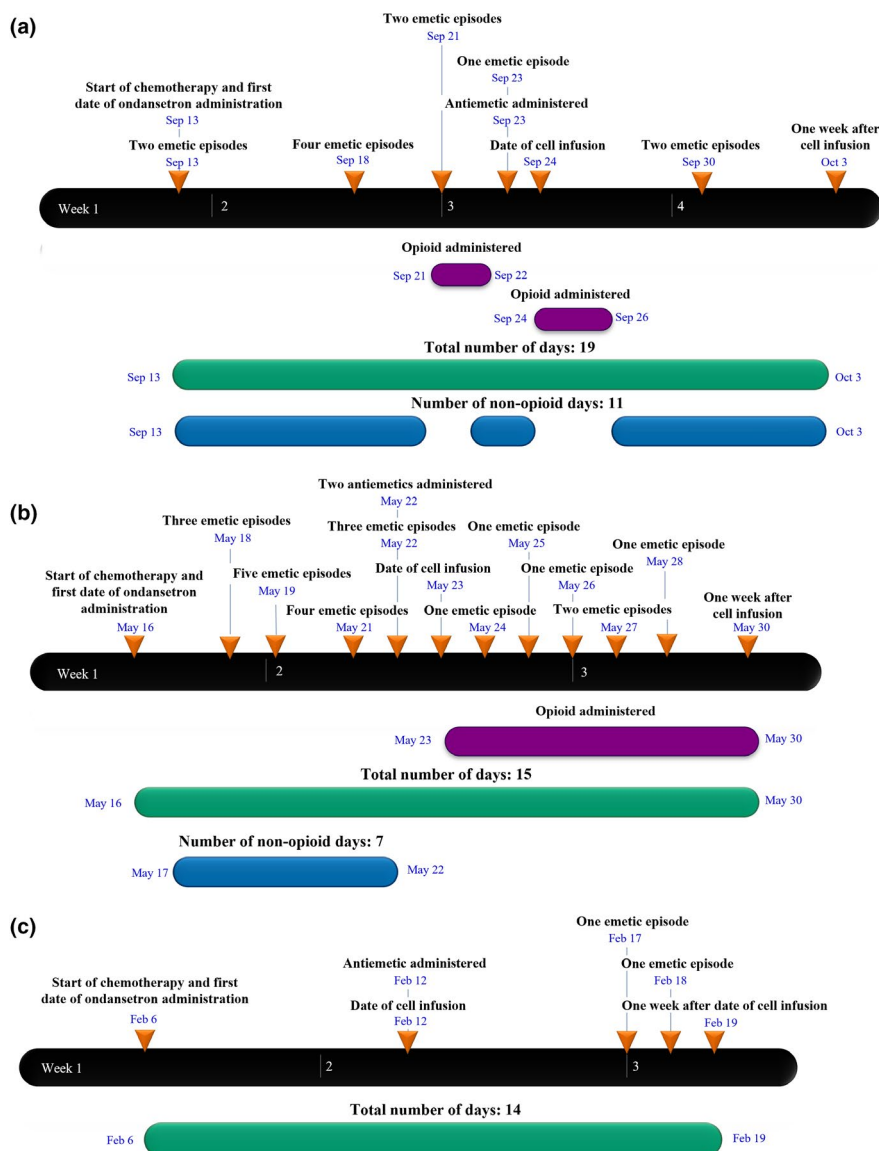
pediatric patients based on CYP2D6 metabolizer status due to a paucity of data. Because there are known differences in the clearance of drugs between adults and children, and because ondansetron is dosed on a milligram per kilogram basis in children compared to adults who all received the same dose, it cannot be assumed that adult data can be extrapolated to a pediatric population.[11,25–28] However, our findings support consideration of CPIC's guidelines in pediatric practice and the use of a non-CYP2D6 metabolized antiemetic, such as granisetron, for the few children known to be CYP2D6 UMs. Nevertheless, further research in children is warranted. Factors besides CYP2D6 metabolizer status have an impact on ondansetron efficacy. Ondansetron is metabolized by enzymes besides CYP2D6, including CYP1A1, CYP1A2, and CYP3A4; there are effects of ontogeny of some of these enzymes.[29,30] An individual's response to ondansetron may be influenced by variants in and

inducers or inhibitors of these other enzymes, which we did not assess.

It was important to separately analyze opioid and non-opioid days as nausea and vomiting is a common side effect with opioids, and opioid-induced nausea and vomiting may not be responsive to ondansetron.[22,31] Therefore, separate summaries of emesis on non-opioid days were performed to remove any contribution of opioids to emetic episodes. When we separated emetic episodes on opioid days versus on non-opioid days, there was indeed a difference in emetic episodes per day on opioid versus non-opioid days. This suggests that failure to account for opioid administration may mask any association between emetic episodes (a biomarker for ondansetron effectiveness) and CYP2D6 metabolizer status.

Chemotherapy emetogenicity, sex, and prior CINV are known to influence the likelihood a patient will experience CINV.[2,32] Patients with a malignant diagnosis
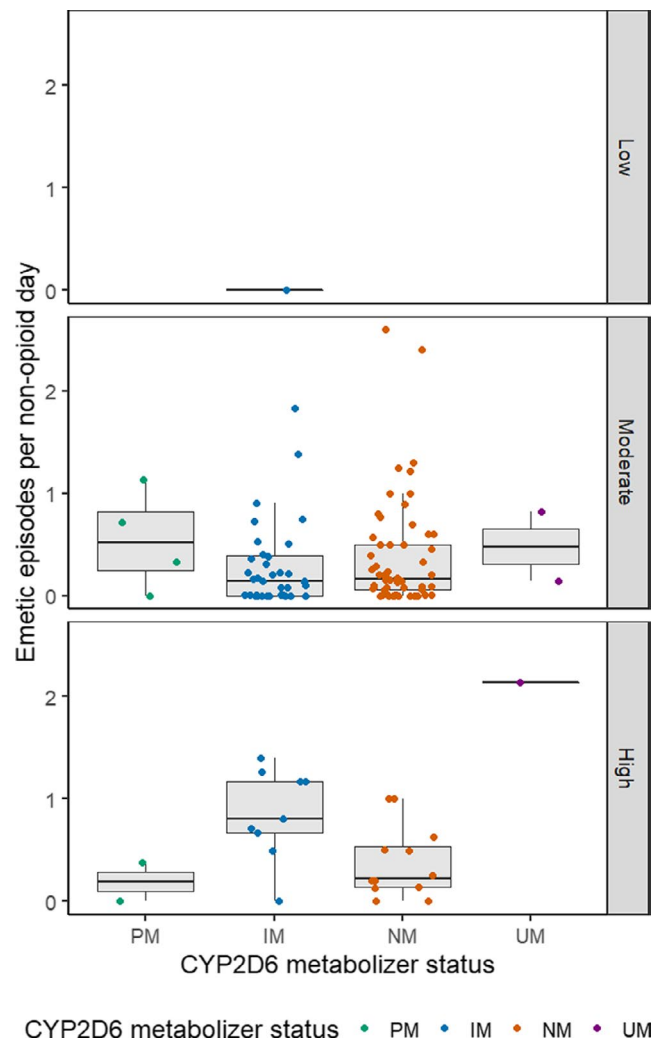
FIGURE 3 Number of emetic episodes per non-opioid day in each metabolizer group, stratified by chemotherapy emetogenicity. IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer

are more likely than patients with a nonmalignant diagnosis to have previously received chemotherapy and are more likely to receive myeloablative regimens, which are highly emetogenic.[33] The chemotherapy emetogenicity contributed to the large amount of variability in number of emetic episodes among patients in our study (range of 0–2.7 emetic episodes per day and range of 0–2.6 emetic episodes per non-opioid days).

Our study was limited by the number of UMs who met eligibility requirements; thus these results should be interpreted with caution. However, the frequency of UMs in our study (2.3%) aligned with the frequency reported by Bell et al. (1–2%) and the frequency reported by Ramsey et al. in a previous study conducted at CCHMC (2.3%).[16,19] The retrospective nature of the study was another limitation. We relied on documented emetic episodes (recorded daily) to capture CINV because nausea is not routinely

recorded in clinical notes in our medical records. Nearly all patients received diphenhydramine (including all 3 UMs), which is possibly a weak CYP2D6 inhibitor,[34–36] and we only accounted for strong/moderate inhibitors in our analysis. The potential for more emetic episodes per non-opioid day in UMs we found would be strengthened by a large prospective study with more UMs.

The genetic testing used to determine patient metabolizer status presented some limitations. The genetic test used for patients in the Bone Marrow Transplantation Program detected 20 *CYP2D6* variants, which account for 93–99% of alleles associated with the four CYP2D6 metabolizer status groups. It is possible that an undetected rare variant was reported as a *1 allele and a patient's assigned metabolizer status did not match their actual CYP2D6 enzyme activity.

In summary, along with factors such as chemotherapy emetogenicity, opioid administration, and type of diagnosis, CYP2D6 metabolizer status was associated with the number of emetic episodes experienced by pediatric HSCT recipients. Pediatric CYP2D6 UMs had an increased number of emetic episodes on non-opioid days compared to other metabolizers. Our findings align with the results of studies conducted in adults, taken together these results suggest CPIC's 5-HT3 antagonist selection guidelines may be appropriate for pediatric practice. Instead of prescribing antiemetics in addition to ondansetron, physicians may want to consider switching pediatric UMs who respond poorly to ondansetron to granisetron to avoid polypharmacy, limit side effects, and better control emesis.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

A.E., A.T.C., L.J.M., C.A.P., P.A.M., and L.B.R. wrote the manuscript. A.E., A.T.C., L.J.M., C.A.P., P.A.M., and L.B.R. designed the research. A.E., A.T.C., and L.B.R. performed the research. A.E., A.T.C., L.J.M., and L.B.R. analyzed the data.

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