Ondansetron Co-Treatment Increases Risk of Cisplatin Nephrotoxicity

Lauren E. Thompson, BS,[1] Xia Wen, PhD,[3,4] Justine Jorgensen, BS,[5] Jordan N. Palan, BS,[1] Cathleen L. Doherty, PhD,[3] Brian T. Buckley, PhD,[3] Edgar A. Jaimes, MD,[5] Lauren M. Aleksunes, PharmD, PhD,[3,4] Melanie S. Joy, PharmD, PhD[1,2]

University of Colorado, Skaggs School of Pharmacy and Pharmaceutical Sciences[1] and Division of Renal Diseases[2], Aurora, CO; Rutgers University, Environmental and Occupational Health Sciences Institute[3] and Ernest Mario School of Pharmacy Department of Pharmacology and Toxicology[4], Piscataway, NJ; Memorial Sloan Kettering Cancer Center, Department of Medicine[5], New York, NY

Background

Cisplatin, a common chemotherapeutic, causes acute kidney injury (AKI) in up to one-third of patients.

Previous reports have indicated that maximum plasma concentration (Cmax) or area under the plasma concentration vs. time curve (AUC) of platinum increase risk of AKI. Ondansetron, a commonly co-prescribed 5-HT$_3$ antagonist antiemetic drug in patients receiving cisplatin, has been associated with enhanced risk of AKI in rodents and retrospective clinical studies. However, to date, there have been no prospective evaluation of AKI risk in patients randomized to specific 5-HT$_3$ antagonist drugs.

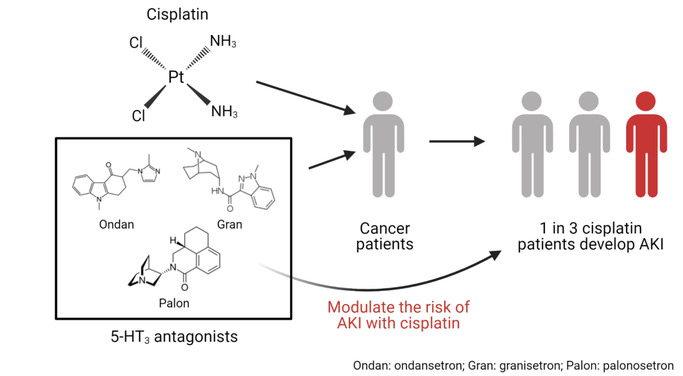
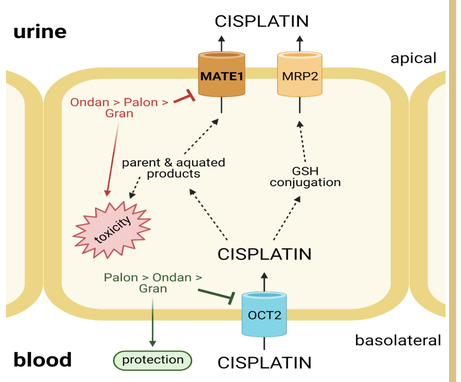


Figure 1. Working model of risk of cisplatin (CIS) nephrotoxicity in patients prescribed 5-HT$_3$ antagonist antiemetics. Cisplatin is taken up into the kidneys by the OCT2 transporter, resulting in cisplatin levels 5x higher in kidney tubule cells than in plasma. Cisplatin forms DNA adducts which ultimately lead to apoptosis, resulting in acute kidney injury (AKI) in about one-third of all cisplatin-treated patients. Previous analyses have suggested that cisplatin patients treated with ondansetron exhibit greater losses of kidney function, as measured by decrease in estimated glomerular filtration rate (eGFR), compared to patients treated with granisetron or palonosetron. It is hypothesized that there is a differential effect of 5-HT$_3$ antagonists on kidney transporters that can modulate the risk of nephrotoxicity due to cisplatin. Previous *in vitro* work by our group (PMID: 34208557) has shown that palonosetron is the strongest inhibitor of OCT2 uptake of ASP+ while ondansetron is the strongest inhibitor of MATE1 ASP+ uptake by over ten-fold compared to the other 5-HT$_3$ antagonists. Together, these data support the hypothesis of higher kidney cisplatin exposure under ondansetron treatment.



5-HT$_3$A	OCT2 IC$_{50}$ (μM)	MATE1 IC$_{50}$ (μM)
Ondansetron	2.6 ± 0.9	**0.1 ± 0.1**
Granisetron	3.8 ± 1.6	5.0 ± 1.1
Palonosetron	2.2 ± 0.3	1.6 ± 0.6

Hypothesis: Cancer patients treated with ondansetron will experience increased cisplatin exposures which predisposes toward renal function decline, as measured by changes in eGFR and urinary biomarkers, compared to patients treated with palonosetron or granisetron.

Methods

- As part of NCT03817970, patients (n=24) prescribed cisplatin (CIS) ≥ 25 mg/m² from the University of Colorado Cancer Center (UCCC) or Memorial Sloan Kettering Cancer Center (MSKCC) were prospectively randomized to one of three 5-HT$_3$ antagonist antiemetic drugs (ondansetron 8 mg p.o./i.v., granisetron 2 mg p.o./i.v., or palonosetron 0.25 mg i.v.).
- Blood and urine were collected for up to 10 days following cisplatin treatment.
- Kidney function was assessed using clinical measurements of serum creatinine (SCr), eGFR, and blood urea nitrogen (BUN) as well as measurements of urinary biomarkers.
- Total platinum (Pt) plasma and urine concentrations were quantified using inductively coupled plasma mass spectrometry (ICP/MS) with LLOQ of 1.0 ng/mL.
- Noncompartmental pharmacokinetic (PK) analysis of total Pt was performed using Certara Phoenix™, with the linear trapezoidal linear interpolation method for AUC calculations.
- PK parameters were compared based on 5-HT$_3$ antagonist treatment using one-way ANOVAs with Tukey-Kramer post-hoc tests using GraphPad Prism (9.4.1).

Results

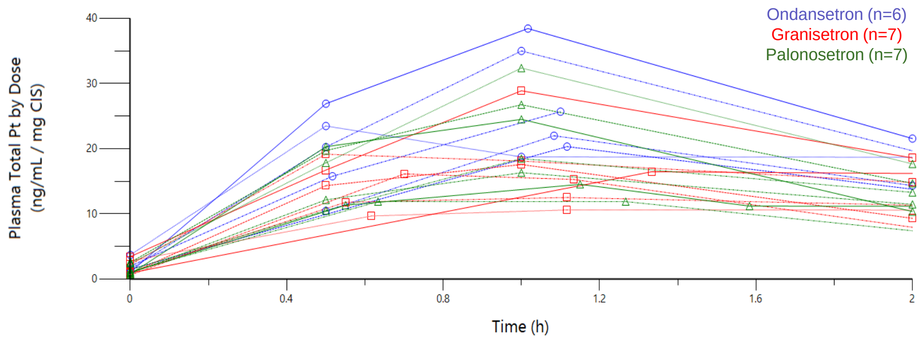


Figure 2. Total platinum (Pt) plasma concentrations, normalized by cisplatin (CIS) dose, following cisplatin treatment. Each line represents an individual patient profile.

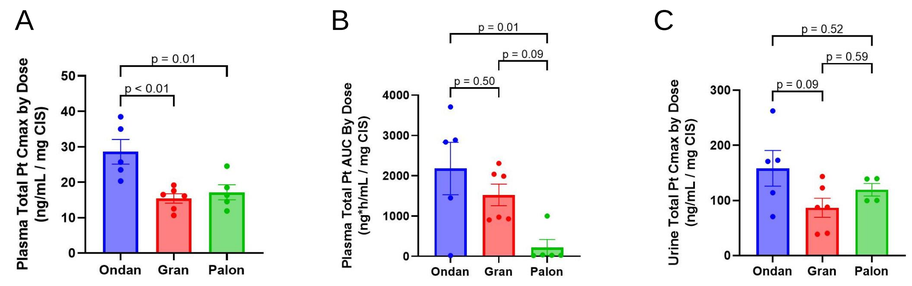


Figure 3. 5-HT$_3$ antagonist antiemetic (ondansetron: blue, granisetron: red, palonosetron: green) prescription altered total platinum (Pt) concentrations. Antiemetic prescription significantly altered patient **A)** plasma maximum concentration (Cmax) of total Pt (p<0.01) and **B)** area under the plasma concentration vs. time curve (AUC) (p=0.02), both normalized by the dose of cisplatin (CIS) given. Patients treated with ondansetron had significantly higher total Pt Cmax levels than patients treated with granisetron (p<0.01) or palonosetron (p=0.01). Patients treated with ondansetron had higher AUCs, or Pt exposures, than patients treated with palonosetron (p=0.01). **C)** Urine maximum concentration (Cmax) of total Pt was not significantly altered by antiemetic prescription (p=0.11), but patients treated with ondansetron exhibited increased urine total Pt Cmax levels compared to patients treated with granisetron (p=0.09). Bars represent mean ± standard error of the mean (SEM).

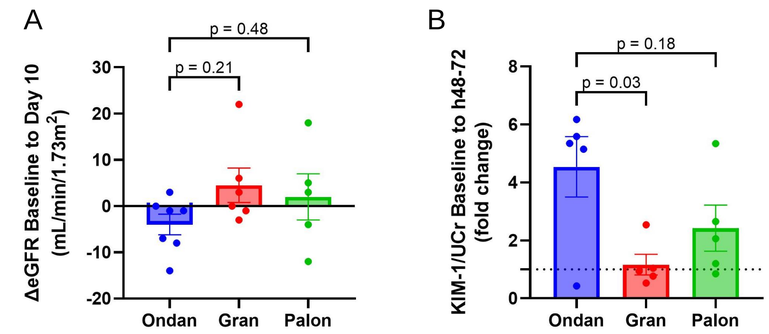


Figure 4. Kidney function change by 5-HT$_3$ antagonist antiemetic (ondansetron: blue, granisetron: red, palonosetron: green) treatment group. Antiemetic prescription may impact **A)** estimated glomerular filtration rate (eGFR) (p=0.22), and significantly alters **B)** urinary KIM-1 normalized by urinary creatinine (UCr) levels (p=0.03) after cisplatin treatment. Patients prescribed ondansetron exhibited decreases in eGFR, indicating decreased kidney function, when compared to patients prescribed granisetron (p=0.21) or palonosetron (p=0.48). Patients treated with ondansetron also exhibited higher KIM-1 levels when compared to patients treated with granisetron (p=0.03) or palonosetron (p=0.18). Bars represent mean ± standard error of the mean (SEM).

Conclusions

- 5-HT$_3$ antagonist antiemetic prescription can modulate total platinum (Pt) exposure and risk of cisplatin nephrotoxicity.
- Ondansetron treatment resulted in higher total platinum Cmax and AUC, increases in urinary KIM-1, and decreases in eGFR or kidney function as compared to granisetron or palonosetron.
- To avoid increased risk of nephrotoxicity by cisplatin, antiemetic treatment with granisetron or palonosetron should be considered, especially in high-risk patients.
- These preliminary data will be validated as the data from additional patients are amassed and the study completed.
- The final study analysis will also incorporate the analysis of several other kidney injury biomarkers.

Acknowledgements

- This study was supported by NIH R21 DK093903, R01 GM123330, T32 ES029074 and CCTSI TL1 TR002533.
- Special thank you to the University of Colorado Cancer Center and Memorial Sloan Kettering Cancer Center for their support.
- The University of Colorado is a Certara Center of Excellence. The Center of Excellence program supports leading institutions with Certara's state-of-the-art model-informed drug development software.
- Figures made using BioRender.com.

References

PMIDs: 20605904, 25165721, 24819883, 34208557, 30220072, 29231123, 35403300.