ONDANSETRON (OND) VERSUS PALONOSETRON (PALO) AS A MARKER OF NON-ADHERENCE TO ANTIEMETIC PROPHYLAXIS GUIDELINES IN HIGHLY EMETOGENIC CHEMOTHERAPY (HEC)

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BACKGROUND

- MASCC and other antiemetic guidelines recommend upfront triple prophylaxis (NK1 receptor antagonist (RA) + 5HT3 RA + dexamethasone) for patients receiving highly emetogenic chemotherapy (HEC).

5HT3 RA = Serotonin Type 3 Receptor Antagonist; HEC = Highly Emetogenic Chemotherapy; LEC = Low Emetogenic Chemotherapy; MEC = Moderate Emetogenic Chemotherapy; NK1 RA = Neurokinin-1 Receptor Antagonist

- Cisplatin and anthracycline + cyclophosphamide (AC) are HEC. Triple prophylaxis was recommended for Carboplatin AUC ≥ 4 per 2016-2017 guidelines.¹⁻³ Carboplatin was previously considered moderately emetogenic.
- Physicians exhibit high variation in HEC guideline adherence, principally regarding inclusion of NK1.⁴
- Whether adherence is associated with selection of the specific 5HT3 agent, and whether there is any impact on patient outcomes from differences in adherence, remain inadequately studied.
- Chemotherapy toxicities such as CINV have taken on increased importance as CMS has included them within the OP-35 oncology outcome measure, based on studies that found CINV among 10 toxicities associated with avoidable acute care in cancer.

OBJECTIVES

- To assess selection of OND vs. PALO in HEC prophylaxis as a marker for non-adherence with antiemetic guidelines (i.e., omission of NK1).
- To compare rates of nausea and vomiting (NV) for OND vs. PALO in HEC.

METHODS

- Data source**
 - Retrospective analysis from 2012-2018.
 - IBM Explorys – large database of electronic medical records, including IV/oral medications.
 - 40 institutions with >350,000 clinicians.
 - Institution-specific data not available.
 - We identified HEC regimens as those where upfront triple prophylaxis is recommended by MASCC and other guidelines, including cisplatin, AC, and carboplatin AUC ≥ 4 .
 - Inclusion criteria was: new HEC courses without any chemotherapy ≤ 90 days prior:
 - Patient courses for ≥ 7 day cycles of cisplatin, AC or other HEC except carboplatin.
 - Carboplatin ≥ 14 day cycles (as a proxy for AUC ≥ 4).
 - At least 2 infusions in a course of therapy.
 - We assigned HEC courses to prescribing oncologists based on encounter frequency in cases where multiple oncologists were associated with the prescription.
 - We categorized 5HT3 use of each physician treating ≥ 5 HEC courses based on their most commonly used 5HT3 agent for prophylaxis (OND or PALO).
 - We evaluated 5HT3 use patterns for each chemotherapy separately for physicians prescribing more than one chemotherapy.
 - We computed the ratio of OND courses to PALO courses for these physicians.
 - We defined antiemetic guideline adherence as triple prophylaxis at chemotherapy initiation. We performed descriptive statistics; differences were evaluated using t-tests and chi-squared tests at a significance level of $\alpha=0.05$.

RESULTS

- We identified 12,262 HEC courses, including 1,455 AC, 2,517 cisplatin and 6,786 carboplatin courses.
- 57% of courses involved physicians whose most common 5HT3 agent was OND (defined as OND comprising >50% of that physician's prophylaxis use relative to PALO). For these physicians the mean OND to PALO ratio was 3.9:1.
- These courses had significantly lower guideline adherence (due to NK1 omission) and higher rates of NV for combined HEC, AC, and carboplatin ($P < 0.001$; **Figures 1, 2**).
 - NV rates for cisplatin did not vary by 5HT3 agent used.
- The remaining 43% of courses involved physicians whose most common 5HT3 was PALO (mean OND:PALO ratio of 0.2:1). These physicians had superior adherence and NV rates, despite involving a slightly higher risk population (younger and/or female; **Table 1**).

DISCUSSION

- As expected, physicians in this study tended to have a majority of their antiemetic prophylaxis involve one of either OND or PALO. This may be due to either physician or institution discretion. Either agent can be used in a compliant regiment with any NK1 and dexamethasone.
- Although physicians and institutions may also have a preference for a specific 5HT3 agent, the decision whether to include any NK1 agent in the prophylaxis regimen for HEC should be independent of the chosen 5HT3 agent (with the exception of the fixed combination netupitant/palonosetron; however, that product was little used prior to 2018). Nevertheless, in this study we did see a statistically significantly higher omission of NK1 agents, in contravention of guidelines, among physicians who predominantly used OND. Choice of the specific NK1 agent did not seem to be a factor, as fosaprepitant was the overwhelming choice of NK1 for both groups.

Table 1: Highly Emetogenic Chemotherapy (HEC) Delivered from 2012-2018

	HEC/Preferred 5HT3							
	Combined HEC		AC		Cisplatin		Carboplatin	
	OND	PALO	OND	PALO	OND	PALO	OND	PALO
Courses	7027	5235	489	966	1511	1006	3972	2814
Age (mean)	62.4	61.0*	55.4	53.8*	61.1	60.9	64.4	63.7*
% female	65%	72%*	98%	99%	41%	45%	70%	74%*
US region, %		*		*		*		*
Midwest	74%	72%	63%	76%	79%	67%	76%	74%
West	15%	12%	27%	13%	9%	14%	14%	10%
South	10%	14%	9%	10%	10%	19%	9%	14%
Northeast	1%	1%	0%	1%	1%	0%	1%	1%
Unknown	1%	1%	1%	1%	0%	0%	0%	1%
Cancer type, %								
Breast	22%	32%*	98%	99%	2%	2%	16%	22%*
Lung	28%	28%	1%	1%	25%	34%*	34%	35%
GI	10%	8%*	<1%	1%	14%	12%*	10%	9%*

* Results with statistically significant differences between OND and PALO have been noted with an asterisk.

Figure 1: Highly Emetogenic Chemotherapy (HEC) Guideline Adherence from 2012-2018

* Statistically significant differences are noted with an asterisk.

** Carboplatin not categorized as HEC prior to 2017; yet 14% received triple prophylaxis.

Figure 2: Highly Emetogenic Chemotherapy (HEC) Nausea and Vomiting from 2012-2018

* Statistically significant differences are noted with an asterisk.

- Since OND is less expensive than PALO, it may be preferred by some physicians or institutions who may deem any potential incremental clinical benefits of PALO to not merit the additional cost, and use of OND can be fully adherent to HEC guidelines when combined with an NK1 agent.
- While causality is not possible to determine from retrospective analyses, there seem to be few possible reasons for omitting the NK1 apart from a desire to avoid cost, since we do not expect that physicians favoring OND are less familiar or comfortable with antiemetic guideline recommendations. Unfortunately, this study also suggests that patients bear a burden of worse outcomes when physicians favoring OND omit NK1.
- For institutions seeking to minimize exposure to avoidable acute care use as measured in CMS' OP-35 oncology outcomes measure, OND use may be a marker for poor adherence to guidelines and risk of symptoms that can impair patient outcomes and Medicare reimbursement.

CONCLUSIONS

- Although HEC antiemetic guidelines call for NK1 use upfront (independent of 5HT3 agent selection), we observed less NK1 use where OND was the preferred 5HT3 agent. This unexplained omission may have caused the observed higher rates of NV with OND.
- Further evaluation should assess whether pharmacy cost is a common driver of OND preference and NK1 omission in HEC.

REFERENCES

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