Antiemetic Guideline Compliance of Neurokinin-1 (NK₁) Receptor Antagonists (RA) in the Highly Emetogenic Chemotherapy Setting

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Eric J. Roeland, MD¹; Kathryn J. Ruddy, MD, MPH²; Thomas W. LeBlanc, MD, MA, MHS³; Gary Binder, MBA⁴; Diana T. Amari, PhD⁵; Andy Surinach⁵; Zheng Wu, MS⁵; Rudolph M. Navari, MD, PhD⁶

¹Massachusetts General Hospital, Boston, MA; ²Mayo Clinic, Rochester, MN; ³Duke University School of Medicine; Duke Cancer Institute, Durham, NC; ⁴Helsinn Therapeutics US, Iselin, NJ; ⁵Genesis Research, Hoboken, NJ; ⁶University of Alabama Birmingham School of Medicine, Birmingham, AL

BACKGROUND

- Antiemetic Chemotherapy-induced nausea and vomiting (CINV) is potentially debilitating for patients and may be so severe that it leads to additional office visits, emergency department (ED) visits, or hospitalizations. In some cases it may prevent patients from completing the full course of chemotherapy [1]. As a result, such patients may have a higher chance of cancer recurrence and shorter survival [2].
- Antiemetic guidelines by MASCC and others consistently recommend a triplet prophylactic regimen of an NK₁RA + 5HT₃RA + dexamethasone [DEX]) for patients receiving highly emetogenic chemotherapy (HEC) [3,4].
- While the American Society of Clinical Oncology (ASCO) recently recognized the development of effective antiemetic therapies among the top five advances in oncology over the last 50 years [ASCO Post 2014], unfortunately studies have demonstrated unsatisfactory adherence with antiemetic guidelines [5,6,7].

METHODS

Objective

- The objective of this study was to evaluate gaps in the real-world utilization of NK₁RA-containing prophylactic antiemetic regimens for patients receiving HEC in the United States (US).

Study Design and Data Source

- A retrospective, non-interventional cohort study was conducted using the Truven Health Analytics MarketScan® database and Medicare supplement, from July 1, 2011 to June 30, 2016 [8].

Study Population

- The study sample included chemotherapy-naïve adult patients with ≥1 claim for intravenous HEC chemotherapy.
- This study focused on the initial HEC chemotherapy cycle for the enrollee after ≥3-months baseline continuous enrollment.
- Patients with a gap between chemotherapy administrations <7 days and/or stem cell transplant (SCT) were excluded.

Measures/Outcomes

- They key outcome measure for this analysis was prophylactic antiemetic use associated with HEC chemotherapy exposure.
- All chemotherapy regimens identified were assigned to a CINV-risk category as specified in the National Comprehensive Cancer Network (NCCN) Guidelines: Antiemesis, Version 2.2017 [4].
- Data for all prophylactic antiemetics were identified based on medical or prescription drug claims on the HEC administration data for intravenous antiemetics, and on or ≤14 days prior for oral antiemetics.
- Patients were stratified by antiemetic regimen group without the requirement for a DEX claim within the defined prophylactic treatment window. Patients were assigned to one of the following antiemetic regimen groups: NK₁RA + 5HT₃RA ± DEX, NK₁RA ± DEX, 5HT₃RA ± DEX, or none ± DEX.
- Only those patients receiving a NK₁RA + 5HT₃RA ± DEX were considered to be guideline compliant.
- Among patients receiving non-compliant therapy of 5HT₃RA ± DEX for their index HEC, the number who subsequently received NK₁RA therapy within the same chemotherapy line was determined.

Statistical Analyses

- All statistical analyses were performed using SAS version 5.4.
- Baseline demographics were analyzed by descriptive statistics.
- Differences between groups were analyzed by chi-square and Cochran-Armitage trend test, as appropriate.

RESULTS

Demographics

- 111,497 chemotherapy-naïve patients receiving HEC chemotherapy were included in the study; 35.1% received carboplatin, 24.1% received anthracycline plus doxorubicin (AC) and 18.1% received cisplatin (Table 1).
- The majority of patients receiving carboplatin (99.3%) had ≥14 days between administrations, a frequency consistent with HEC classified as AUC ≥ 4.
- Among all HEC-receiving patients, 24.0% were ≤50 years and 24.3% were >65 years (Table 1). AC-receiving patients were more likely to be young (35.3% ≤50 years. Most patients were female (70.7%) (Table 1).

Table 1. Baseline Demographic Characteristics by Chemotherapy Regimen (2011-2016)								
Characteristic	All HEC		Carboplatin		AC		Cisplatin	
	N	%	N	%	N	%	N	%
All patients	111,497	100%	39,080	100%	26,893	100%	20,176	100%
18-50	26,756	24.0%	6,358	16.3%	9,503	35.3%	3,442	17.1%
51-55	16,065	14.4%	4,872	12.5%	4,498	16.7%	3,095	15.3%
56-60	20,355	18.3%	7,101	18.2%	4,616	17.2%	4,344	21.5%
61-65	21,253	19.1%	8,050	20.6%	4,212	15.7%	4,560	22.6%
66-70	9,672	8.7%	4,065	10.4%	1,575	5.9%	2,049	10.2%
>70	17,396	15.6%	8,634	22.1%	2,489	9.3%	2,686	13.3%
Female	78,823	70.7%	27,932	71.5%	22,724	84.5%	8,773	43.5%
18-50	21,690	19.5%	5,397	13.8%	8,649	32.2%	1,900	9.4%
51-55	12,390	11.1%	3,948	10.1%	4,072	15.1%	1,400	6.9%
56-60	14,523	13.0%	5,371	13.7%	3,988	14.8%	1,816	9.0%
61-65	14,379	12.9%	5,649	14.5%	3,400	12.6%	1,858	9.2%
66-70	6,074	5.4%	2,594	6.6%	1,184	4.4%	805	4.0%
>70	9,767	8.8%	4,973	12.7%	1,431	5.3%	994	4.9%
Male	32,674	29.3%	11,148	28.5%	4,169	15.5%	11,403	56.5%
18-50	5,066	4.5%	961	2.5%	854	3.2%	1,542	7.6%
51-55	3,675	3.3%	924	2.4%	426	1.6%	1,695	8.4%
56-60	5,832	5.2%	1,730	4.4%	628	2.3%	2,528	12.5%
61-65	6,874	6.2%	2,401	6.1%	812	3.0%	2,702	13.4%
66-70	3,598	3.2%	1,471	3.8%	391	1.5%	1,244	6.2%
>70	7,629	6.8%	3,661	9.4%	1,058	3.9%	1,692	8.4%

Antiemetic Guidelines Compliance

- From 2011 to 2016, 44.8% of all HEC patients received guideline-recommended prophylactic antiemetic therapy (NK₁RA + 5HT₃RA ± DEX) for their initial cycle of chemotherapy (Table 2).
- Compliance rates were lower for carboplatin-receiving patients (25.9%) than for AC-receiving or cisplatin-receiving patients (70.7% and 72.0%, respectively).
- Very few patients received compliant prophylactic antiemetic therapy of 5HT₃RA + olanzapine ± DEX (n=137, 0.12% of all HEC patients).
- Among all HEC patients receiving non-compliant prophylactic antiemetic therapy, nearly all non-compliant regimens involved a 5HT₃RA ± DEX (50.4%); 0.7% involved a NK₁RA ± DEX and 4.1% were non/other ± DEX (Table 2). This was consistent among non-compliant patients receiving carboplatin, AC or cisplatin (70.8%, 27.0% and 24.9% received a 5HT₃RA ± DEX, respectively).

Table 2. Guideline Compliance by Antiemetic Regimen (2011-2016)								
Antiemetic Regimen	All HEC		Carboplatin		AC		Cisplatin	
	N	%	N	%	N	%	N	%
NK ₁ RA + 5HT ₃ RA ± DEX	49,916	44.8%	10,131	25.9%	18,999	70.7%	14,523	72.0%
5HT ₃ RA ± DEX	56,214	50.4%	27,655	70.8%	7,253	27.0%	5,022	24.9%
NK ₁ RA ± DEX	830	0.7%	122	0.3%	251	0.9%	319	1.6%
None/Other ± DEX	4,537	4.1%	1,172	3.0%	390	1.5%	312	1.6%

- Most patients received DEX within the antiemetic prophylactic window (NK₁RA + 5HT₃RA, 92.1%; NK₁RA, 62.0%; 5HT₃RA, 86.3%).
- Among all HEC patients, guideline compliance improved approximately 1.7 percentage points annually from 2011 to 2016.
- Compliance declined with older age among both males (53.6% in men 18-50 years and 45.0% in men >70 years) and females (61.8% in women 18-50 years and 34.3% in women >70 years) (p < 0.0001) (Figure 1).
- This age-associated decline in compliance was more pronounced among women: Women aged 18–50 years receiving HEC-chemotherapy were the sex/age group most likely to have received guideline compliant antiemetic prophylaxis (61.8%); whereas women aged >70 years were least likely to receive compliant prophylaxis (34.3%) (Figure 1).
- Among patients receiving non-compliant prophylaxis of 5HT₃RA ± DEX at chemotherapy induction (50.4% of all HEC patients), 11.0% received an NK₁RA in a subsequent cycle within the same line of chemotherapy. These rates were 22.0% for AC, 20.0% for cisplatin, and consistently and substantially higher in females than males (Figure 2).

CONCLUSIONS

- <50% of all patients treated with HEC received guideline-recommended prophylaxis of a NK₁RA-containing regimen from 2011–2016. Consistent with the findings of previous studies in the US and EU, this large study revealed that substantial improvement in complying with antiemetic guideline recommendations is needed for patients receiving HEC, and in particular for those patients being treated with carboplatin, AC, or cisplatin [5,6,7].
- Absence of upfront NK₁RA use at chemotherapy initiation commonly results in subsequent NK₁RA use, especially among females, mostly likely due to breakthrough CINV.
- This discrepancy seen between the carboplatin-treated patients (only 25.9% received an NK₁RA-regimen) versus AC (70.7%) or cisplatin (70.2%) is likely due to the perception and understanding that this chemotherapy agent was, until 2017, considered to be moderately emetogenic by most antiemetic treatment guidelines.
- The findings of this large study emphasize the importance of clinicians/organizations streamlining practices to improve compliance with evidence-based antiemetic guideline recommendations for upfront prophylaxis of an NK₁RA triplet regimen in the HEC setting. Adopting an action plan to ensure 1) use of the best antiemetics available, 2) active compliance with guidelines, and 3) diligent monitoring of CINV symptoms between office visits may be the best way to optimize patients' quality of life during cancer treatment [7].

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