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Safety Profile of HTX-019 Administered as an Intravenous Infusion in Patients With Cancer

A Retrospective Analysis

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ABSTRACT

HTX-019 is a neurokinin 1 receptor antagonist approved for prevention of acute and delayed chemotherapy-induced nausea and vomiting in patients with cancer receiving moderately and highly emetogenic chemotherapy. When administered as a 30-minute intravenous (IV) infusion, HTX-019 has displayed a tolerable and favorable safety profile in healthy subjects. This is the first study to evaluate the safety profile of multiple HTX-019 infusions in patients with cancer. This retrospective analysis shows that HTX-019 administered via IV infusion has a favorable safety profile in patients with cancer, and no new treatment-emergent adverse events were identified.

Key words: aprepitant, CINV, HTX-019, intravenous infusion, IV, NK-1 RA, safety, TEAE

HTX-019 (CINVANTI [aprepitant] injectable emulsion; Heron Therapeutics, Inc., San Diego, CA) is a substance P neurokinin 1 (NK-1) receptor antagonist (RA) used in combination with other antiemetics as part of guideline-recommended regimens for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients with cancer receiving highly emetogenic (HEC) or moderately emetogenic chemotherapy (MEC).[1-4] HTX-019 is a synthetic surfactant-free and polysorbate 80-free aprepitant emulsion that was initially approved by the US Food and Drug Administration (FDA) in November 2017 for administration as a 30-minute intravenous (IV) infusion approximately 30 minutes before chemotherapy.[5] This approval was based on bioequivalence studies showing that a single dose of HTX-019 130 mg administered as a 30-minute IV infusion was bioequivalent to and safer than a single dose of fosaprepitant 150 mg IV infused over 20 minutes (study 106) and 30 minutes (study 104).[6,7] Subsequently, the HTX-019 130 mg IV was included as a category 1 recommendation by the National Comprehensive Cancer Network.[1]

Because studies 104 and 106 were conducted in healthy subjects, and safety was a secondary end point in both studies, a study of safety in patients with cancer receiving chemotherapy was desirable. The present retrospective analysis is the first to evaluate the safety of HTX-019 administered by 30-minute IV infusion per the labeled indication in patients with cancer receiving multiple cycles of HEC or MEC at the New York Cancer Center.

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METHODS

This retrospective analysis of patient information was undertaken from March 2017 through July 2018 at 24 sites of the New York Cancer Center in New York, NY. The analysis included patients who had an Eastern Cooperative Oncology Group performance status of 0 to 3, received MEC or HEC chemotherapy regimens, and received antiemetic treatment with the aprepitant injectable emulsion HTX-019 130 mg as part of a 3-drug regimen with a 5-hydroxytryptamine type 3 RA (granisetron extended release, palonosetron, granisetron, or granisetron and palonosetron) and dexamethasone. The investigator included only patients who received at least 4 doses of HTX-019 to limit the use of other chemotherapy drugs. The safety profile of HTX-019 was defined as the total number of treatment-emergent adverse events (TEAEs) and the number of treatment-related TEAEs (related to HTX-019 administration) observed in patients who received the 30-minute IV infusion.

Patient information was collected by initiating queries within the electronic medical records to identify patients who were prescribed HTX-019. This information was then verified against the medication administration record for each patient to confirm that the doses were used. The occurrence of infusion-site adverse events (ISAEs) or hypersensitivity reactions (HSRs) was identified by reviewing detailed nursing notes taken 0 to 30 minutes and 30 to 60 minutes after HTX-019 administration; the occurrence of other TEAEs later, before the next chemotherapy cycle, was similarly identified. Records were searched over multiple chemotherapy cycles for documented codes, nursing codes, and physician notes relating to ISAEs (pain, erythema, swelling, hives, phlebitis, superficial thrombosis, and delayed infusion) or HSRs (flushing, hypotension, bronchospasm, and cardiac dysfunction).

RESULTS

Patients

A total of 864 HTX-019 IV infusions were administered to 147 patients (74 men, 73 women) with a median age of 66 years (range 25 to 89 years), most (92%) of whom were white (Table 1). The most common diagnoses were colorectal cancer (29%), lung cancer (23%), and breast cancer (12%). A mean of 6 cycles of chemotherapy were administered; 71 patients (48%) received an HEC regimen, the most common being carboplatin with paclitaxel (n = 25), and 76 patients (52%) received an MEC regimen, the most common being fluorouracil with oxaliplatin (n = 19). The routes of administration were central (54%) and peripheral (46%), and most (81%) patients did not receive previous radiation therapy (Table 1).

Safety and Tolerability of HTX-019 Injections

HTX-019 administered as a 30-minute IV infusion was safe and well tolerated. Nine (6%) of 147 patients experienced a

TABLE 1

Patient Demographics and Baseline Characteristics

Demographics	N = 147
Median age (range), y	66 (25-89)
Sex, n (%)	
Male	74 (50)
Female	73 (50)
Race, n (%)	
White	135 (92)
Black or African American	8 (5)
Asian	1 (1)
Other	3 (2)
Emetogenic risk, n (%)	
HEC	71 (48)
MEC	76 (52)
ECOG PS at baseline, n (%)	
0	116 (79)
1	22 (15)
2	8 (5)
3	1 (1)
Type of cancer, n (%)	
Colorectal	43 (29)
Lung	34 (23)
Breast	17 (12)
Pancreatic	10 (7)
Esophageal	10 (7)
Other[a]	33 (23)
Route of administration, n (%)	
Central	80 (54)
Peripheral	67 (46)
Previous radiation therapy, n (%)	
No	119 (81)
Yes	28 (19)
5-HT_3 RA therapy, n (%)	
GERSC	99 (67)
Palonosetron	43 (29)
Granisetron	1 (1)
GERSC and palonosetron	1 (1)
None	3 (3)
HTX-019 doses, n (mean)	864 (6)

Abbreviations: 5-HT_3 RA, 5-hydroxytryptamine type 3 (serotonin) receptor antagonist; ECOG PS, Eastern Cooperative Oncology Group performance status; GERSC, granisetron extended release subcutaneous; HEC, highly emetogenic therapy; MEC, moderately emetogenic therapy; y, years.

[a]Astrocytoma, basal cell carcinoma, B-cell lymphoma, bladder, cardiac neoplasm, cervical, stomach, head and neck, uterine, leukemia/lymphoma, non-Hodgkin's lymphoma, ovarian, parotid gland neoplasm, prostate, renal, pelvic, bile duct, multiple myeloma, salivary gland, and T-cell lymphoma.

total of 14 TEAEs. The most common TEAE was feeling hot, which occurred in 4 patients (3%), followed by dizziness and pruritus, each of which occurred in 2 patients (1%; Table 2). None of the TEAEs were considered serious or led to study drug discontinuation or study withdrawal—all were mild in severity and resolved by the end of the study.

Furthermore, none of the TEAEs was attributed to HTX-019 administration. The 4 cases in which patients reported feeling hot occurred between 64 minutes and 268 minutes after HTX-019 administration had begun. The 2 cases of pruritus occurred 180 minutes and 329 minutes after the start of HTX-019 administration, and the 2 cases of dizziness occurred at 50 minutes and 180 minutes after the start of HTX-019 infusions. The rest of the TEAEs (erythema, nausea, shortness of breath, chest tightness, lower back pain, or general discomfort) occurred between 60 minutes and 298 minutes after HTX-019 administration had begun. Based on the timing of chemotherapy administration, which began ≥50 minutes after the start of HTX-019 infusions, and the occurrence of TEAEs (all reported after start of chemotherapy administration), no TEAEs were deemed by the investigator to be related to the HTX-019 infusions (Table 2), and no ISAEs were reported in any patients.

DISCUSSION

In this retrospective analysis, HTX-019 displayed a tolerable safety profile when administered as a 30-minute IV infusion for CINV prophylaxis in patients with cancer receiving HEC or MEC. Overall, 9 patients experienced a total of 14 TEAEs, the most common being feeling hot (3%). Notably, all of the reported TEAEs occurred after chemotherapy administration had begun (50-329 minutes after the start of HTX-019 infusions); therefore, no TEAEs were deemed by the investigator to be related to HTX-019 administration. These results are similar to those observed in healthy subjects.[6,7] In study 104, the proportion of subjects reporting TEAEs was smaller with HTX-019 30-minute infusions (21%) compared with fosaprepitant 20-minute infusions (28%).[6] Similarly, in study 106, the proportion of subjects reporting TEAEs was smaller with HTX-019 30-minute infusions (13%) compared with fosaprepitant 20-minute infusions (30%).[7] In addition, both studies showed a smaller proportion of study drug-related TEAEs with HTX-019 versus fosaprepitant (study 104, 15% vs 28%; study 106, 10% vs 27%).[6,7]

In the current analysis, TEAEs occurred in 6% of patients, none related to HTX-019 injections. No new TEAEs were observed when HTX-019 was administered before HEC or MEC. The results of this retrospective analysis at the New York Cancer Center demonstrate the tolerability and safety of HTX-019 administered as an IV infusion in patients with cancer. This study strengthens the idea that the safety of HTX-019 is attributable to its polysorbate 80- and synthetic surfactant-free formulation. Limitations of this study include its retrospective nature, with certain types of adverse events not analyzed or accounted for, because the study was designed to detect and analyze specific HSRs and ISAEs based on predetermined nursing and medical documentation.

Treatment with other NK-1 RA IV formulations (fosaprepitant and rolapitant) has been associated with HSRs, including anaphylaxis and anaphylactic shock, and ISAEs.[8,9] Specifically, treatment with fosaprepitant has resulted in ISAEs including infusion-site pain, erythema, swelling, venous hardening or induration, and phlebitis or thrombophlebitis, all of which may be associated with polysorbate 80.[9] Moreover, rolapitant IV, approved in late 2017, contains polyoxyl 15 hydroxystearate, which may be associated with several HSRs. Soon after the formulation's approval, the FDA issued a MedWatch safety alert to health care providers warning against HSRs that may occur during or after rolapitant IV administration. This alert[10] was followed by the manufacturer suspending the rolapitant IV formulation in February 2018.[11] Given these HSRs and ISAEs, a more tolerable NK-1 RA formulation, such as HTX-019, would be a valuable addition to antiemetic regimens.

TABLE 2

Summary of Treatment-Emergent Adverse Events

Category	30-min IV Infusion HTX-019 130 mg (N = 147)
Patients with ≥1 TEAE, n (%)	9 (6)
Total number of TEAEs	14
HTX-019-related TEAEs	0
TEAE, n (%)	
Feeling hot	4 (3)
Dizziness	2 (1)
Pruritus[a]	2 (1)
Nausea	1 (1)
Shortness of breath	1 (1)
Feeling weird	1 (1)
Chest tightness	1 (1)
Lower back pain	1 (1)
Erythema	1 (1)

Abbreviations: IV, intravenous; min, minute; TEAE treatment-emergent adverse event.
[a]Pruritus includes itch and itchy scalp.

CONCLUSION

This retrospective analysis further demonstrates the favorable safety profile of HTX-019 administered as a 30-minute IV infusion. The findings are of clinical relevance for nurses because they suggest that a tolerable NK-1 RA formulation of HTX-019 may provide a safe and effective addition to antiemetic regimens for preventing CINV in patients with cancer.

REFERENCES

1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: antiemesis—version 1.2019. https://www.nccn.org/professionals/physician_gls/default.aspx#supportive. Published February 28, 2019. Accessed April 25, 2019.
2. Herrstedt J, Roila F, Warr D, et al. 2016 updated MASCC/ESMO consensus recommendations: prevention of nausea and vomiting following high emetic risk chemotherapy. *Support Care Cancer*. 2017;25(1):277-288.
3. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017;35(28):3240-3261.
4. Roila F, Warr D, Hesketh PJ, et al. 2016 updated MASCC/ESMO consensus recommendations: prevention of nausea and vomiting following moderately emetogenic chemotherapy. *Support Care Cancer*. 2017;25(1):289-294.
5. Heron Therapeutics. Cinvanti (aprepitant) injectable emulsion, for intravenous use [prescribing information]. San Diego, CA: Heron Therapeutics; 2019.
6. Ottoboni T, Keller MR, Cravets M, Clendeninn N, Quart B. Bioequivalence of HTX-019 (aprepitant IV) and fosaprepitant in healthy subjects: a phase I, open-label, randomized, two-way crossover evaluation. *Drug Des Devel Ther*. 2018;12:429-435.
7. Ottoboni T, Lauw M, Keller MR, et al. Safety of HTX-019 (intravenous aprepitant) and fosaprepitant in healthy subjects. *Future Oncol*. 2018;14(27):2849-2859.
8. Varubi (rolapitant) tablets, for oral use. Varubi® (rolapitant) injectable emulsion, for intravenous use [prescribing information]. Waltham, MA: Tesaro Inc; 2018.
9. Merck & Co. Emend (fosaprepitant) for injection, for intravenous use [prescribing information]. Whitehouse Station, NJ: Merck & Co; 2019.
10. US Food and Drug Administration. Anaphylaxis, anaphylactic shock and other serious hypersensitivity reactions associated with use of VARUBI® (rolapitant) injectable emulsion. https://www.fda.gov/media/110258/download. Published January, 2018. Accessed April 25, 2019.
11. Tesaro website. Tesaro announces fourth-quarter and full-year 2017 operating results. https://www.globenewswire.com/newsrelease/2018/02/27/1396449/0/en/TESARO-Announces-Fourth-Quarter-and-Full-Year-2017-Operating-Results.html. Accessed July 24, 2019.