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HALT-D: A Phase II Evaluation of Crofelemer for the Prevention and Prophylaxis of Diarrhea in Patients With Breast Cancer on Pertuzumab-Based Regimens

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Abstract

Approximately 40% to 80% of patients receiving pertuzumab-directed therapy for human epidermal growth factor receptor 2 (HER2)-positive breast cancer will develop chemotherapy-induced diarrhea (CID). Loperamide and octreotide are frequently used to treat CID after diarrhea occurs, but neither is used prophylactically or targets the underlying mechanism. Previous studies suggest blocking epidermal growth factor receptor may cause excess chloride secretion, resulting in diarrhea. Crofelemer is derived from the red latex of the *Croton lechleri* tree, blocks gastrointestinal cystic fibrosis transmembrane regulator and calcium-activated chloride channels, and is U.S. Food and Drug Administration approved for relief of diarrhea in HIV/AIDS patients on anti-retroviral therapy. Crofelemer is not systemically absorbed, has relatively few side effects, and presents a targeted approach at preventing CID in patients receiving pertuzumab-based therapy. HALT-D (DiarrHeA Prevention and Prophylaxis with Crofelemer in HER2-Positive Breast Cancer Patients Receiving Trastuzumab, Pertuzumab, and Docetaxel or Paclitaxel with or without Carboplatin, NCT02910219) is a phase II, randomized, open-label trial that aims to recruit 46 patients from 3 MedStar sites. Adults with HER2-positive breast cancer being treated with trastuzumab, pertuzumab, and docetaxel or paclitaxel (THP) or trastuzumab, pertuzumab, docetaxel, and carboplatin (TCHP) will be randomized to receive crofelemer or no medication for diarrhea prophylaxis. The primary endpoint is incidence of all grade diarrhea for 2 consecutive days during cycles 1 to 2 of THP or TCHP. Secondary endpoints include overall incidence, duration, and severity of diarrhea; time to onset of diarrhea; use of other anti-diarrheal medications; stool frequency and consistency; and quality of life. HALT-D will provide important information about the feasibility and tolerability of crofelemer in preventing diarrhea for patients receiving THP or TCHP.

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Disclosure

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Keywords

Breast cancer; Chemotherapy induced diarrhea; Crofelemer; HER2; Pertuzumab

Introduction

Approximately one-quarter of patients with breast cancer have human epidermal growth factor 2-positive (HER2⁺) disease.¹ Pertuzumab-based regimens are U.S. Food and Drug Administration (FDA)-approved for use in the neoadjuvant and metastatic settings and are currently being studied in the adjuvant setting.^{2–4} All grade chemotherapy-induced diarrhea (CID) is seen in up to 80% of patients, with 3% to 11.8% of patients who are receiving trastuzumab, pertuzumab, and docetaxel or paclitaxel (THP) or trastuzumab, pertuzumab, docetaxel, and carboplatin (TCHP) experiencing grade 3 and above diarrhea.^{2–5} But even grade 1 to 2 diarrhea can cause electrolyte imbalance, dehydration, and significantly impact a patient's quality of life. Current CID guidelines recommend loperamide or octreotide after diarrhea occurs, but very few studies have looked at anti-diarrheal agents in the prophylactic setting, and none has looked at a targeted approach.^{6–10}

Rationale for Use of Crofelemer

In addition to HER2, there are 3 other receptors in the epidermal growth factor receptor (EGFR)/HER family (EGFR or HER1, HER3, and HER4). Previous studies have shown that CID in pertuzumab-based regimens may be because of EGFR down-regulation and blockade leading to excess chloride secretion and thus secretory diarrhea.^{8–12} No anti-diarrheal medication used for the treatment of CID, including loperamide and octreotide, offers a targeted approach.

Crofelemer is an extract from the red latex of the *Croton lechleri* tree found in South America.¹³ It is FDA-approved for treatment of diarrhea in HIV/AIDS patients on anti-retroviral therapy.¹⁴ Crofelemer acts only lumenally in the bowel owing to its size and polarity and is a dual inhibitor of the calcium-activated chloride channel and the cystic fibrosis transmembrane regulator, 2 of the 3 channels that control gastrointestinal chloride efflux. Given its mechanism of action, crofelemer may provide a targeted approach at preventing CID in patients with breast cancer receiving THP or TCHP chemotherapy.

HALT-D (DiarrHeA Prevention and PropPhylaxis With Crofelemer in HER2-Positive Breast Cancer Patients Receiving Trastuzumab, Pertuzumab, and Docetaxel or Paclitaxel With or Without Carboplatin) Study Design

The primary aim of the HALT-D (NCT02910219) study is to compare the incidence of all-grade diarrhea for at least 2 consecutive days between patients who receive prophylaxis with crofelemer and those who do not receive any prophylactic medication, which is the current standard of care. Patients who will receive THP or TCHP for their breast cancer will be randomly assigned (1:1) to 1 of these 2 treatment arms and stratified to THP with docetaxel,

THP with paclitaxel, or TCHP (Figure 1). Diarrhea grading will be based on the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0.

In addition to the incidence of all-grade diarrhea, HALT-D will also look at the duration of diarrhea, the time to onset to the first diarrhea episode, the use of anti-diarrhea rescue medications, stool frequency and consistency as measured by the Bristol Stool scale, and quality of life, as assessed by the Functional Assessment of Chronic Illness Therapy – Diarrhea (FACIT-D) total and diarrhea subset scores.

Treatment

Patients randomized to the crofelemer arm will receive crofelemer 125 mg twice daily during cycles 1 and 2 of THP or TCHP chemotherapy. During cycle 3, they will not receive crofelemer, but will still be followed for diarrhea. Patients randomized to the control arm will not receive any diarrhea prophylactic medication. However, patients in both arms are eligible to receive anti-diarrhea rescue medications (loperamide, tincture of opium, etc) should they develop diarrhea.

Key Inclusion Criteria

The study is open to male and female patients 18 years of age who have a pathologically confirmed diagnosis of HER2⁺ breast cancer of any stage and are scheduled to receive at least 3 consecutive cycles of THP or TCHP. Patients may have received previous treatment for their breast cancer without limits on prior lines of therapy, and patients with brain metastases on current treatment are allowed. Patients must have an Eastern Cooperative Oncology Group performance status of 0 to 2 and a negative pregnancy test for women of childbearing potential. Patients may simultaneously enroll on HALT-D and other studies.

Key Exclusion Criteria

As HALT-D is seeking to determine the incidence of diarrhea, patients with ongoing irritable bowel syndrome or colitis or those with any type of ostomy, total colectomy, or fecal incontinence are excluded from the study. Furthermore, patients on active laxative, anti-diarrheal, antibiotic, anti-fungal, anti-parasite, or anti-viral medication use are excluded. Those who have radiation-induced bowel changes, are planning on receiving radiation therapy to the abdomen or pelvis while on study, or have had major abdominal or pelvic surgery within the past 6 months are excluded. Finally, patients with inadequate organ function for starting THP or TCHP will be excluded.

Statistical Considerations

A total of 46 patients will be accrued across 3 MedStar cancer sites in the greater Washington, DC area. The number and percent of patients who experience diarrhea of any grade for 2 or more consecutive days (felt to be definitely, probably, or possibly owing to THP or TCHP) during cycle 1 and 2 will be summarized with 2-sided 90% confidence interval overall and by treatment assignment, and compared between treatment arms using

the Fisher exact test. The analysis population is defined as all randomized patients who complete 2 cycles of THP or TCHP chemotherapy.

We anticipate recruiting 2 to 3 patients per month across the study sites combined, with the accrual duration lasting approximately 17 to 26 months. We anticipate enrolling the first patient in October 2016. The last patient will be enrolled in the winter of 2018, with a final analysis completed in the spring of 2019.

Conclusions

Current CID guidelines recommend treating diarrhea with anti-diarrheal medications such as loperamide or octreotide only after diarrhea develops. Very few studies have looked at preventing CID before it occurs. Crofelemer blocks chloride channels in the gastrointestinal tract, potentially providing a targeted approach at preventing pertuzumab-mediated diarrhea. The HALT-D study has been designed to look at the efficacy of crofelemer in the prophylactic setting. This will be the first time crofelemer has been studied in conjunction with chemotherapy, and we hope the results from this trial can help contribute to the standard of care management of CID in patients with breast cancer.

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Figure 1.

HALT-D Study Design

Abbreviations: BID = twice a day; HER2 = human epidermal growth factor receptor 2; TCHP = trastuzumab, pertuzumab, docetaxel, and carboplatin; THP = trastuzumab, pertuzumab, and docetaxel or paclitaxel.